

Management of chronic obstructive pulmonary disease (COPD)

Peter G. Gibson, Senior Staff Specialist, Department of Respiratory & Sleep Medicine, John Hunter Hospital, Conjoint Associate Professor, School of Medical Practice, Faculty of Medicine, University of Newcastle, and Director, Asthma, Infection and Immunology Research Group, Hunter Medical Research Institute, Newcastle, New South Wales

SYNOPSIS

The expiratory airflow obstruction that characterises chronic obstructive pulmonary disease is usually progressive over time and caused by emphysema, obliterative bronchiolitis, and mucus hypersecretion. Stopping smoking is the only measure that slows the progression of chronic obstructive pulmonary disease, and smokers should be encouraged to stop at all stages of the disease. The effects of medication are limited, and need to be balanced against cost and adverse effects. Bronchodilators, given by puffer and spacer rather than by nebuliser, are effective. Avoid inhaled corticosteroids unless there is associated asthma. Pulmonary rehabilitation leads to important improvements in quality of life. Influenza vaccination is helpful. Comorbidity from cardiac disease and sleep disordered breathing are common and can be effectively treated. New therapies under evaluation include lung volume reduction surgery, non-invasive ventilation, and anti-inflammatory drugs.

Key words: smoking, beta agonists, corticosteroids, oxygen.

(Aust Prescr 2001;24:152-5)

Introduction

In chronic obstructive pulmonary disease (COPD), airflow is obstructed during expiration. This increases the work of breathing and causes dyspnoea. In contrast to asthma, the airflow obstruction is not reversible and usually progresses over time. There are several mechanisms of airflow obstruction in COPD. Chronic bronchitis results in hypersecretion of mucus which fills and obstructs the airway lumen. Inflammation and fibrosis of the airway mucosa and surrounding tissue (obliterative bronchiolitis) cause airway wall thickening. Emphysema causes loss of the alveolar attachments which normally hold the airway open.

The aims of management in COPD are therefore to:

- reduce airflow obstruction
- reduce symptoms and improve quality of life
- prevent or reduce secondary medical complications.

The management of COPD involves ongoing assessment and treatment of each of these problems over a long period of time.

A consultation checklist is given in Table 1 – try ‘SMOKES’ in the fight against COPD.

Smoking cessation

Smoking cessation is the only measure known that slows the progression of COPD so it should be considered at all stages of the disease. Medical advice, behavioural management, nicotine replacement therapy and bupropion are important components of effective smoking cessation programs. Even intermittent quitting is better than continued smoking.¹ Successful approaches assess the readiness to quit of the patient, provide individualised education and behavioural strategies, and use nicotine replacement to manage nicotine withdrawal symptoms.

Health professionals have a social responsibility to reduce smoking. They are eyewitnesses to the suffering caused by smoking and need to communicate this to the community, rather than become cynical at the practices of the tobacco industry.

The role of medication

The disease causes chronic disability and the efficacy of drug therapy is limited. Consequently, there is the potential for polypharmacy with its attendant difficulties with compliance, drug interactions and adverse effects. Frequently, resources are allocated to drugs with limited efficacy, while patients are denied interventions such as pulmonary rehabilitation that make a real difference to their quality of life.

Table 1

SMOKES, a consultation checklist for chronic obstructive pulmonary disease

- S:** smoking cessation
- M:** medication – inhaled bronchodilator, vaccines (influenza, pneumococcus), stop unnecessary treatment (nebuliser, inhaled corticosteroids)
- O:** oxygen – is it needed?
- K:** komorbidity – cardiac dysfunction, sleep apnoea, osteoporosis, depression, asthma
- E:** exercise and rehabilitation
- S:** surgery – lung volume reduction surgery, single-lung transplantation

Table 2

Efficacy of interventions for stable chronic obstructive pulmonary disease

	<i>Reduce airflow obstruction</i>	<i>Reduce symptoms</i>	<i>Reduce secondary medical complications</i>
Smoking cessation	+	+	+
Medications			
Short-acting beta agonist	+	+	-
Anticholinergic	+	+	-
Long-acting beta agonist			
COPD with asthma	+	+	-
COPD without asthma	(+)	(+)	-
Antibiotics	-	-	-
Inhaled corticosteroids	-	-	-
Mucolytics	-	-	-
Oxygen	-	-	+
Rehabilitation	+	+	-

Results of systematic reviews or large randomised clinical trials, accessible by searching the Cochrane Library for 'COPD' and examining the Cochrane Database of Systematic Reviews and Controlled Clinical Trials Register

+ clinical benefit demonstrated

- clinical benefit not demonstrated. This could be due to ineffective treatment or incomplete evaluation.

(+) statistically significant, but clinical significance unclear

Table 2 shows the effects of medication in stable COPD, based on the results of systematic reviews or large randomised-controlled trials. These results need to be contrasted with a recent audit which showed that 69% of patients were using regular inhaled corticosteroid (a treatment unlikely to be beneficial in COPD), whereas only 27% had completed pulmonary rehabilitation and only 40% had received influenza vaccination.² We should stop using ineffective treatment and start using effective management techniques.

Bronchodilators

In an airway that is already narrowed by COPD, normal bronchomotor tone may have an exaggerated constrictor effect on airway narrowing. Bronchodilators relax airway smooth muscle and partially improve airflow obstruction. Short-acting beta agonists improve dyspnoea and airflow obstruction without clear benefit on exercise performance.³ These drugs can be used alone or in combination with anticholinergics, where an additional benefit may be achieved.

Anticholinergic drugs such as ipratropium bromide improve dyspnoea, airflow obstruction and quality of life in COPD. They have not been shown to improve long-term outcome.

Patients with COPD also benefit from long-acting beta agonists if they have significant bronchodilator reversibility, i.e. asthma. (Most clinicians accept that a bronchodilator response of >15% baseline FEV₁ or >200 mL FEV₁ or >10% predicted FEV₁ indicates asthma.) The role of these drugs in COPD without asthma is less clear⁴, and their adverse effects remain a concern. Cardiac arrhythmias can be problematic in severe COPD and long-acting beta agonists may cause a prolonged reduction in serum potassium and potentiate ventricular and atrial premature beats.⁵ Careful consideration of the costs and

benefits of long-acting beta agonists in patients without asthma is needed before using these drugs in COPD.

Theophyllines are also effective bronchodilators, however adverse effects are frequent. For every seven patients treated, one develops nausea and vomiting (NNV, number needed to vomit, 7).

Drug delivery

Stop using nebulisers!

Drug delivery, by pressurised metered dose inhaler and spacer, has equal efficacy to nebulised treatment. It is cheaper and avoids some of the uncommon adverse effects reported with nebulised therapy: paradoxical bronchoconstriction, glaucoma and systemic effects such as dry mouth and urinary retention.

Antibiotics

The impaired airway defences in COPD allow colonisation by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Typically, these organisms cannot be eradicated from the diseased airway, and so antibiotics are of little use in stable COPD. Some patients with recurrent infective bronchitis (more than three times a year) and persistent purulent sputum may benefit from three months treatment with tetracycline.

COPD is exacerbated by several different causes. Antibiotics are of little benefit if the exacerbation does not have the features of infection. When there is evidence of infection with increased sputum volume, or purulence, fever or a new infiltrate on chest X-ray, then antibiotics can shorten the duration of illness.⁶ *Streptococcus* is sensitive to penicillin. *Haemophilus* responds to amoxycillin, although between 15% and 30% are penicillin resistant. Macrolides have limited clinical

efficacy in exacerbations due to haemophilus. Moraxella is resistant to penicillins. Amoxicillin with clavulanic acid or doxycycline are effective against each organism.

Annual vaccination against influenza is recommended. Pneumococcal vaccine should be given every five years.

Corticosteroids

Oral corticosteroids are beneficial during exacerbations of COPD, leading to a reduced time in hospital. They have a very limited role in stable COPD. The typical neutrophilic bronchitis that is seen in COPD is not reversed by corticosteroid treatment. *In vitro* evidence raises the possibility that steroids may exaggerate this response by inhibiting neutrophil apoptosis.

About one in five patients responds to a short course of prednisolone. Typically, these patients have an eosinophilic bronchitis⁷ as seen in asthma, and this accounts for their favourable response. In order to find who will benefit, patients require a formal trial of prednisolone 30–40 mg daily for 14 days with objective assessment of their response by spirometry. Responders can be considered to have the same pattern of airway inflammation as in asthma, and are treated with ongoing inhaled and oral corticosteroids as required. Steroids should be stopped in non-responders.

Inhaled corticosteroids

Many patients with COPD are prescribed inhaled corticosteroids. The benefits are questionable⁸, whereas the potential for adverse effects is real. A review of 10 trials of short-term inhaled corticosteroids in COPD found no significant improvement in lung functions.⁹ In mild COPD, two large trials have shown that inhaled corticosteroids do not prevent long-term progression of the disease. There may be an initial improvement in lung function, but this is not sustained. One study conducted in patients with more severe COPD showed a reduction in moderate to severe exacerbations, however methodological problems have limited the interpretation of these data. Regular inhaled corticosteroids in stable COPD without an asthmatic component are of questionable efficacy and have the potential for adverse effects. The cost is also considerable.

Mucolytics

Treating mucus hypersecretion shortens the duration of disability during exacerbations by about 0.65 days per month. The clinical significance and cost-effectiveness of mucolytics are unclear.² Physiotherapy is effective in removing excessive airway secretions but has no clear effect on lung function.

Oxygen

Long-term domiciliary oxygen therapy can reduce mortality in hypoxaemic COPD. Consequently it is important to identify and treat patients with hypoxia (by blood gases or pulse oximetry) as well as the effects of hypoxia (polycythaemia, cor pulmonale).¹⁰

Rehabilitation

Behavioural management of chronic dyspnoea and the resultant physical deconditioning are important aspects of management. Pulmonary rehabilitation programs address these issues and lead to increased exercise tolerance, increased exercise ability, reduced dyspnoea and improved quality of life.¹¹ The key parts of pulmonary rehabilitation are:

- exercise training
- education
- psychosocial/behavioural intervention
- outcome assessment.

Each part should be systematically addressed in all patients with moderate or severe COPD. This can be achieved by referral to an established program, or by a series of consultations between the patient, doctor and allied health staff. Although low body weight is associated with impaired pulmonary function, clinical trials have not shown that nutritional supplements are beneficial.

Comorbidity

COPD is a long-term problem, and patients may acquire several other conditions during their life. These may be exacerbated by COPD, affected by drugs for COPD, or cause symptoms that increase disability in COPD. A high index of suspicion needs to be maintained for comorbid conditions in COPD.

Left ventricular dysfunction is common and can cause an exacerbation of dyspnoea. Primary cardiac disease (coronary artery disease, hypertension) may coexist with COPD and a dilated right ventricle can impair left ventricular diastolic function.

Sleep disordered breathing can be a problem in COPD, particularly during REM sleep. Sleep studies are indicated when there is a suspicion of sleep apnoea, or when cor pulmonale and/or polycythaemia are present but not explained by daytime oxygen levels.

Anxiety and depression occur in up to 30% of patients with COPD, leading to impaired functional capacity and quality of life. In one study of severe COPD, walking distance and functional ability were better related to the presence of depression than the degree of airflow obstruction.

Osteoporosis complicates COPD and corticosteroid therapy. A crush fracture or rib fracture constitute major events for a person with COPD. Prevention of osteoporosis is important and starts with avoiding unnecessary treatment, particularly corticosteroids.

Novel approaches

Lung volume reduction surgery involves resection of emphysematous parts of the lungs, typically in the upper lobes. This reduces hyperinflation and improves the mechanical efficiency of the respiratory muscles. Potentially suitable patients are those who have completed a pulmonary rehabilitation program, have predominantly upper lobe emphysema with little comorbidity, who accept that the

long-term outcomes and comparative efficacy are unknown, and who understand and accept the local perioperative mortality rate (5–15% is considered acceptable).¹²

Non-invasive ventilation is a major advance for the management of hypercapnic/acidotic exacerbations of COPD. The benefits in stable COPD with respiratory failure are being evaluated in an Australian multicentre trial. Several experimental drugs are being evaluated for their effects on airway inflammation and extracellular matrix destruction in COPD.

Conclusion

COPD is a chronic and disabling condition caused by smoking. Disability can be minimised by a systematic approach to management that emphasises the use of safe, effective medications, withdraws unsafe or ineffective therapy, and attends to the effects of physical deconditioning and psychosocial distress through rehabilitation.

E-mail: mdpgg@mail.newcastle.edu.au

REFERENCES

- Murray RP, Anthonisen NR, Connett JE, Wise RA, Lindgren PG, Greene PG, et al. Effects of multiple attempts to quit smoking and relapses to smoking on pulmonary function. Lung Health Study Research Group. *J Clin Epidemiol* 1998;51:1317-26.
- Poole PJ, Bagg B, Brodie SM, Black PN. Characteristics of patients admitted to hospital with chronic obstructive pulmonary disease. *N Z Med J* 1997;110:272-5.
- Sestini P, Renzoni E, Robinson S, Poole P, Ram FSF. Short-acting beta 2 agonists for stable chronic obstructive pulmonary disease (Cochrane Review). In: *The Cochrane Library*, 3, 2001. Oxford: Update Software.
- Appleton S, Smith B, Veale A, Bara A. Long-acting beta2-agonists for chronic obstructive pulmonary disease (Cochrane Review). In: *The Cochrane Library*, 3, 2001. Oxford: Update Software.
- Cazzola M, Imperatore F, Salzillo A, Di Perna F, Calderaro F, Imperatore A, et al. Cardiac effects of formoterol and salmeterol in patients suffering from COPD with preexisting cardiac arrhythmias and hypoxemia. *Chest* 1998;114:411-5.
- Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196-204.
- Pizzichini E, Pizzichini MM, Gibson P, Parameswaran K, Gleich GJ, Berman L, et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. *Am J Respir Crit Care Med* 1998;158:1511-7.
- Kerstjens H, Postma D. Chronic obstructive pulmonary disease. In: *Clin Evid* 2000;3:701-11.
- Postma DS, Kerstjens HA. Are inhaled glucocorticosteroids effective in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 1999;160(5 Suppl 2):S66-71.
- Cramond T. Home oxygen. *Aust Prescr* 1996;19:69-71.
- Pulmonary rehabilitation—1999. American Thoracic Society. *Am J Respir Crit Care Med* 1999;159:1666-82.
- Snell GI, Peacock M, Garrett J. Lung volume reduction surgery: the Thoracic Society of Australia and New Zealand. *Int Med J* 2001;31:112-5.

FURTHER READING

See resources on the following web sites:
<http://www.aacvpr.org>
<http://www.goldcopd.com>

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 158)

- Inhaled corticosteroids produce a sustained improvement in lung function in most patients with chronic obstructive pulmonary disease.
- Giving a beta agonist by nebuliser is more effective than giving it by metered dose inhaler and spacer.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Board believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Board is prepared to do this. Before new drugs are prescribed, the Board believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Cetrorelix acetate

Cetrotide (Serono)

vials containing 250 microgram or 3 mg as powder for reconstitution

Approved indication: assisted reproduction

Australian Medicines Handbook Section 10.6.3

Luteinising hormone has an important role in the menstrual cycle. In assisted reproduction programs a premature surge in luteinising hormone can cause ovulation, and therefore disrupt the collection of oocytes. This surge can be prevented by antagonising luteinising hormone releasing hormone (LHRH).

Cetrorelix competes with LHRH for binding sites in the

pituitary gland. This reduces the secretion of luteinising hormone and follicle stimulating hormone. A 250 microgram dose is injected every day starting five or six days after ovarian stimulation is begun. These injections continue until the day before ovulation is induced. A single large dose (300 mg) can be used to suppress ovulation for at least four days.

Analogues of gonadotrophin-releasing hormones have also been used to prevent surges of luteinising hormone. (Prolonged administration of an analogue agonist eventually reduces gonadotrophin production.) Cetrorelix has therefore been compared with the LHRH agonists such as triptorelin and buserelin. While cetrorelix was as efficacious as the agonists it has the advantage of a more immediate action.