The COPDX Plan:
Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2009

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The Thoracic Society of Australia and New Zealand

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Foreword

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a major cause of disability, hospital admission and premature death. More than 600,000 Australians are estimated to have COPD[1] and, as the population ages, the burden of COPD is likely to increase. In Australia, COPD is the fifth greatest contributor to the overall burden of disease accounting for 3.6% of disability-adjusted life years (DALY) in 2003. In New Zealand, 1996 data indicated that for men COPD was the second most common cause of years lost to disability (YLD) and for women the seventh most common cause. 2003 estimates suggest that the prevalence of COPD in New Zealand women had increased substantially with COPD possibly being the leading overall cause of death and disability[2]. COPD ranks fourth among the common causes of death in Australian men and sixth in women. In New Zealand, it ranks third in men and fourth in women[3]. COPD is commonly associated with other diseases including heart disease, lung cancer, stroke, pneumonia and depression.

Smoking is the most important risk factor for COPD. In 2004-05, 24.2% of Australian males and 18.4% of Australian females over the age of 18 years smoked[1]. Smoking-related diseases have increased substantially in women, and death rates from COPD in women are expected to rise accordingly. The death rate from COPD among indigenous Australians is five times that for non-indigenous Australians, and smoking is a leading cause of healthy years lost by indigenous people both in Australia and New Zealand.

COPD costs the Australian community an estimated $818–$898 million annually[4]. This is a conservative estimate, based on 1993–1994 figures extrapolated to the year 2001. The addition of hidden costs, such as those related to carer burden, loss of productivity from absenteeism and early retirement, could increase the estimate to more than $1 billion per annum.

Health systems in Australia and New Zealand have historically been oriented toward the treatment of acute diseases and/or acute exacerbations of chronic diseases with a dominant reactive episodic model of care. The challenges posed by the increasing burden of chronic diseases on health systems require development of health service models that have a fundamentally different orientation toward anticipatory and proactive care in addition to acute reactive care not only for individuals with a particular chronic condition (like COPD), but also for individuals with multiple morbidities[5].

Wagner and colleagues have articulated domains for system reform in their Chronic Care Model. These include Delivery System Design (e.g. multi-professional teams, clear division of labour, acute vs. planned care); Self Management Support (e.g. systematic support for patients / families to acquire skills and confidence to manage their condition); Decision Support (e.g. evidence-based guidelines, continuing professional development programs) and Clinical Information Systems (e.g. recall reminder systems and registries for planning care).

Much can be done to improve quality of life, increase exercise capacity, and reduce morbidity and mortality in individuals who have COPD. This Australian and New Zealand guideline is written as a decision support aid primarily for general practitioners and other primary health care clinicians managing people with established COPD. It is regularly updated as new evidence is published.

The key recommendations are summarised in the "COPDX Plan":

Confirm diagnosis,

Optimise function,

Prevent deterioration,

Develop a self-management plan and manage

e**X**acerbations.

Professor Nicholas Glasgow (on behalf of the COPD Evaluation Committee)

The COPD guidelines

THESE GUIDELINES are the outcome of a joint project of the Thoracic Society of Australia and New Zealand and the Australian Lung Foundation. The guidelines aim to:

- effect changes in clinical practice based on sound evidence; and
- shift the emphasis from a predominant reliance on pharmacological treatment of COPD to a range of interventions which include patient education, self-management of exacerbations and pulmonary rehabilitation.

These guidelines deal mainly with the management of established disease and exacerbations. However, this is only one element of the COPD Strategy of the Australian Lung Foundation, which has the long-term goals of:

- primary prevention of smoking;
- improving rates of smoking cessation;
- early detection of airflow limitation in smokers before disablement; and
- improved management of stable disease and prevention of exacerbations.

In May 2001 a multidisciplinary steering committee was convened by the Thoracic Society of Australia and New Zealand (TSANZ) and the Australian Lung Foundation in accordance with the National Health and Medical Research Council recommendations for guideline development.[6] The Committee agreed to use the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Report[7] as the prime evidence base, together with systematic reviews and meta-analyses from the Cochrane Database. The GOLD Report, released in April 2001, was produced by an international panel of experts in collaboration with the United States National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO). The levels of evidence in the current guidelines were assigned according to the system developed by the NHLBI (**Box 1**). Any changes to the guidelines have been based on subsequent versions of the GOLD report and on the results of systematic reviews or consistent evidence from well conducted randomised controlled trials.

The Guidelines Steering Committee supervised the development of specific items such as the COPDX Plan and a management handbook for primary care clinicians. Drafts of these documents were widely circulated to key stakeholder groups and professional organisations. In addition, the draft guidelines were published on the Internet (http://www. lungnet.com.au/copd.html), and access to them was advertised in a national newspaper. The draft guidelines were circulated to all members of the TSANZ and Australian Divisions of General Practice. All comments received were reviewed by the Steering Committee. The Guidelines were then published as a supplement to The Medical Journal of Australia in March 2003.

The Steering Committee then resolved to establish a COPD Guidelines Implementation Committee and a Guidelines Evaluation Committee. The terms of reference of the Evaluation Committee included scientific assessment of the impact of the guidelines on clinical practice and rigorous examination of the relevant medical literature to ensure the guidelines remain up to date. Any suggested modifications have been circulated to members of the COPD Coordinating Committee and other key stakeholders prior to ratification. This version of the guidelines has been submitted to the COPD Special Interest Group of the Thoracic Society of Australia and New Zealand for endorsement.

Associate Professor David K McKenzie and Professor Peter Frith.

Principal authors and members of the COPD Implementation Committee.

July 2005

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Levels of evidence

THE KEY RECOMMENDATIONS and levels of evidence incorporated in the COPDX guidelines were originally based largely on the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which used the evidence ranking system of the US National Heart, Lung and Blood Institute (NHLBI).[7] The NHLBI scheme is shown in **Box 1**. For comparison, the National Health and Medical Research Council (NHMRC)[6] levels of evidence are also shown, along with the equivalent NHLBI categories.

For this update, the COPD Evaluation Committee reclassified NHLBI level A as NHMRC level I and NHLBI level B as NHMRC level II evidence. All citations to NHLBI level C were individually reviewed and reclassified as NHMRC level II, III-2, III-3 or IV evidence. On closer examination, some references originally classified as level C were actually considered level D. As NHLBI level D is not recognised in the NHMRC classification, these levels were removed whilst the bibliographic citations were retained.

Box 1: Levels of evidence

a) National Heart, Lung, and Blood Institute (NHLBI) categories

NHLBI category	Sources of evidence	Definition
A	Randomised controlled trials (RCTs) extensive body of data	Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomised controlled trials (RCTs) limited body of data	Evidence is from endpoints of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, category B pertains when few randomised trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Non-randomised trials, observational studies	Evidence is from outcomes of uncontrolled or non-randomised trials or from observational studies.
D	Panel consensus, judgement	The panel consensus is based on clinical experience or knowledge that does not meet the above criteria.

b) National Health and Medical Research Council (NHMRC) levels of evidence and corresponding National Heart, Lung, and Blood Institute categories

NHLBI category	NHMRC level	Basis of evidence
A	I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
B	II	Evidence obtained from at least one properly designed randomised controlled trial.
C	III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
C	III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
C	III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel group.
C	IV	Evidence obtained from case series, either post-test or pre-test/post-test.

Summary of the COPDX guidelines

C: Confirm diagnosis and assess severity	Evidence level
• Smoking is the most important risk factor in the development of COPD	I
• Consider COPD in all smokers and ex-smokers over the age of 35 years	II
• The diagnosis of COPD rests on the demonstration of airflow limitation which is not fully reversible	II
• If airflow limitation is fully or substantially reversible, the patient should be treated as for asthma	
• Consider COPD in patients with other smoking-related diseases	I
O: Optimise function	
• Inhaled bronchodilators provide symptom relief and may increase exercise capacity	I
• Long term use of systemic glucocorticoids is not recommended	I
• Inhaled glucocorticoids should be considered in patients with severe COPD with frequent exacerbations	II
• Pulmonary rehabilitation reduces dyspnoea, fatigue, anxiety and depression, improves exercise capacity, emotional function and health-related quality of life and enhances patients' sense of control over their condition	I
• Pulmonary rehabilitation reduces hospitalisation and has been shown to be cost-effective	II
• Prevent or treat osteoporosis	I
• Identify and treat hypoxaemia and pulmonary hypertension	
• In selected patients, a surgical approach may be considered for symptom relief	III-2
P: Prevent deterioration	
• Smoking cessation reduces the rate of decline of lung function	I
• Treatment of nicotine dependence is effective and should be offered to smokers in addition to counselling	I
• Influenza vaccination reduces the risk of exacerbations, hospitalisation and death	I
• Mucolytics may reduce the frequency and duration of exacerbations	II
• Long-term oxygen therapy (>15h/day) prolongs life in hypoxaemic patients (Pao2 <55mmHg, or 7.3kPa)	I
D: Develop support network and self-management plan	
• COPD imposes handicaps which affect both patients and carers	II
• Enhancing quality of life and reducing handicap requires a support team	
• Patients and their family/friends should be actively involved in a therapeutic partnership with a range of professional disciplines	II
• Multidisciplinary care plans and individual self-management plans may help to prevent or manage crises	III-2
• Patients who take appropriate responsibility for their own management may have improved outcomes	III-1
X: Manage eXacerbations	
• Early diagnosis and treatment may prevent admission	III-2
• Multidisciplinary care may assist home management	II
• Inhaled bronchodilators are effective treatments for acute exacerbations	I
• Systemic glucocorticoids reduce the severity of and shorten recovery from acute exacerbations	I
• Exacerbations with clinical signs of infection (increased volume and change in colour of sputum and/or fever, leukocytosis) benefit from antibiotic therapy	II
• Controlled oxygen delivery (28%, or 0.5-2.0L/min) is indicated for hypoxaemia	
• Non-invasive positive pressure ventilation is effective for acute hypercapnic ventilatory failure	I
• Involving the patient's general practitioner in a case conference and developing a care plan may facilitate early discharge	

C: Confirm diagnosis and assess severity

Smoking is the most important risk factor in the development of COPD[8],[9] [evidence level I]

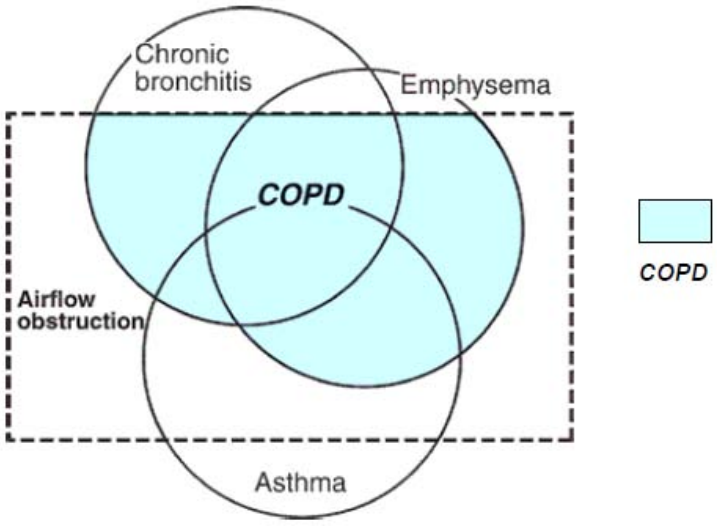
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation which is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases[10]. In clinical practice, diagnosis is usually based on:

- A history of smoking, or exposure to other noxious agents
- $FEV_1/FVC<0.7$ post-bronchodilator

Small-airway narrowing (with or without chronic bronchitis) and emphysema caused by smoking are the common conditions resulting in COPD. Chronic bronchitis is daily sputum production for at least three months of two or more consecutive years. Emphysema is a pathological diagnosis, and consists of alveolar dilatation and destruction. Breathlessness with exertion, chest tightness and wheeze are the results of airway narrowing and impaired gas exchange. The loss of lung elastic tissue in emphysema may result in airway wall collapse during expiration, leading to dynamic hyperinflation and consequent increased work of breathing.

The irreversible component of airflow limitation is the end result of inflammation, fibrosis and remodelling of peripheral airways. Airflow limitation leads to non-homogeneous ventilation, while alveolar wall destruction and changes in pulmonary vessels reduce the surface area available for gas exchange. In advanced COPD there is a severe mismatching of ventilation and perfusion leading to hypoxaemia. Hypercapnia is a late manifestation and is caused by a reduction in ventilatory drive. Pulmonary hypertension and cor pulmonale are also late manifestations, and reflect pulmonary vasoconstriction due to hypoxia in poorly ventilated lung, vasoconstrictor peptides produced by inflammatory cells and vascular remodelling.[7] The clinical features and pathophysiology of COPD can overlap with asthma, as most COPD patients have some reversibility of airflow limitation with bronchodilators. By contrast, some non-smokers with chronic asthma develop irreversible airway narrowing. The overlap between chronic bronchitis, emphysema and asthma and their relationship to airflow obstruction and COPD are illustrated in **Box 2**. Patients with chronic bronchiolitis, bronchiectasis and cystic fibrosis may also present with similar symptoms and partially reversible airflow limitation.

Box 2: Overlap of bronchitis, emphysema and asthma within chronic obstructive pulmonary disease (COPD)



This non-proportional Venn diagram shows the overlap of chronic bronchitis, emphysema and asthma within COPD. Chronic bronchitis, airway narrowing and emphysema are independent effects of cigarette smoking, and may occur in various combinations. Asthma is, by definition, associated with reversible airflow obstruction. Patients with asthma whose airflow obstruction is completely reversible do not have COPD. In many cases it is impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity.

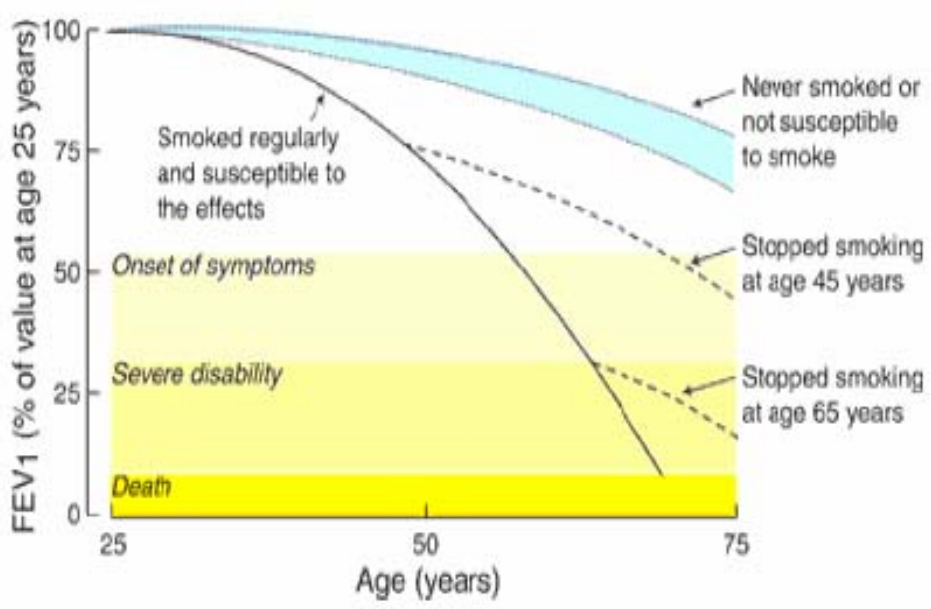
C1. Aetiology and natural history

Cigarette smoking is the most important cause of COPD.[8],[9] There is a close relationship between the amount of tobacco smoked and the rate of decline in forced expiratory flow in one second (FEV_1), although individuals vary greatly in susceptibility.[8] Around half of all smokers develop some airflow limitation, and 15%–20% will develop clinically significant disability.[8] Smokers are also at risk of developing lung cancer, and cardiovascular disease such as ischaemic heart disease and peripheral vascular disease.

In susceptible smokers cigarette smoking results in a steady decline in lung function, with a decrease in FEV_1 of 25–100mL/year.[8] While smoking cessation may lead to minimal improvements in lung function, more importantly it will slow the rate of decline in lung function and delay the onset of disablement. At all times smoking cessation is important to preserve remaining lung function.[8]

Impairment increases as the disease progresses, but may not be recognised because of the slow pace of the disease. The time course of development of COPD and disability and the influence of smoking cessation are illustrated in Box 3.

Box 3: Time-course of chronic obstructive pulmonary disease (COPD)[8]



The figure (adapted from Fletcher C and Peto R. The natural history of chronic airflow obstruction. BMJ 1977;1:1645-1648 and reproduced with permission from the BMJ Publishing Group) shows the rate of loss of forced expiratory flow in one second (FEV_1) for a hypothetical, susceptible smoker, and the potential effect of stopping smoking early or late in the course of COPD. Other susceptible smokers will have different rates of loss, thus reaching "disability" at different ages. The normal FEV_1 ranges from below 80% to above 120%, so this will affect the starting point for the individual's data (not shown).

In addition to cigarette smoking, there are a number of other recognised risk factors for COPD[11] (see Figure 3-1 below adapted from GOLD 2006). COPD almost always arises from a gene environment interaction. The best characterised genetic predisposition is $alpha_1$ antitrypsin deficiency, but multiple other genes each make a small contribution and further investigation is required. The risk of COPD is related to the total burden of inhaled particles[11] and oxidative stress in the lung. Occupational dust exposure might be responsible for 20 – 30% of COPD. This has long been recognised in underground miners, but recently biological dust has also been identified as a risk factor, particularly in women.[12] Fortunately the air quality in most Australian cities is relatively good and cooking with biomass fuels (wood, dung etc) is uncommon. Failure to achieve maximum lung function increases the risk of COPD in later life. The role of gender is uncertain. Beyond the age of 45-50 years, female smokers appear to experience an accelerated decline in FEV_1 compared with male smokers[13] [evidence level II]. Nor is it known whether the increased risk among lower socioeconomic groups is due to greater exposure to pollution, poorer nutrition, more respiratory infection or other factors.[11]

Figure 3-1. Risk Factors for COPD[11]

Genes
Exposure to particles
Tobacco smoke
Occupational dusts, organic and inorganic
Indoor air pollution from heating and cooking with bio-mass in poorly vented dwellings
Outdoor air pollution
Lung Growth and Development
Oxidative stress
Gender
Age
Respiratory infections
Socioeconomic status
Nutrition
Comorbidities
Asthma

Although FEV_1 has long been accepted as the single best predictor of mortality in population studies in COPD[8], [14] recent studies have suggested various other indices, which may also predict mortality. In patients with established COPD, degree of hyperinflation as measured by inspiratory capacity/ total lung capacity (IC/TLC) ratio was independently associated with all cause and COPD mortality.[15] The 6 minute walk distance (6MWD), peak VO_2 during a cardiopulmonary exerise test, body mass index and dyspnoea score (measured with the modified Medical Research Council Scale) have all been shown to predict mortality better than FEV_1 in patients with established disease. Several of these latter indices incorporated together in a single score, the BODE index (BMI, degree of Obstruction as measured by FEV_1, Dyspnoea score and Exercise capacity measured by 6 minute walk) strongly predicted mortality.[16] Nonetheless, FEV_1 continues to have utility as a predictor of all-cause mortality in COPD. In one study that followed patients after acute exacerbations, the five-year survival rate was only about 10% for those with an FEV_1 <20% predicted, 30% for those with FEV_1 of 20%–29% predicted and about 50% for those with an FEV_1 of 30%–39% predicted.[17] Patients with an FEV_1 <20% predicted and either homogeneous emphysema on HRCT or a DLCO <20% predicted are at high risk for death after LVRS and unlikely to benefit from the intervention.[18]

Continued smoking and airway hyperresponsiveness are associated with accelerated loss of lung function.[19] However, even if substantial airflow limitation is present, cessation of smoking may result in some improvement in lung function and will slow progression of disease[19],[20]

The development of hypoxaemic respiratory failure is an independent predictor of mortality, with a three-year survival of about 40%.[21] Long term administration of oxygen increases survival to about 50% with nocturnal oxygen[21] and to about 60% with oxygen administration for more than 15 hours a day[22](see also **Section P**).

Admission to hospital with an infective exacerbation of COPD complicated by hypercapnic respiratory failure is associated with a poor prognosis. A mortality of 11% during admission and 49% at two years has been reported in patients with a partial pressure of carbon dioxide (PCO_2) >50mmHg.[17] For those with chronic carbon dioxide retention (about 25% of those admitted with hypercapnic exacerbations), the five-year survival was only 11%.[17]

C2. Diagnosis

C2.1 History

Consider COPD in all smokers and ex-smokers over the age of 35 years[8] [evidence level II]

The main symptoms of COPD are breathlessness, cough and sputum production.[23] Patients often attribute breathlessness to ageing or lack of fitness. A persistent cough, typically worse in the mornings with mucoid sputum, is common in smokers. Other symptoms such as chest tightness, wheezing and airway irritability are common.[24] Acute exacerbations, usually infective, occur from time to time and may lead to a sharp deterioration in coping ability. Fatigue, poor appetite and weight loss are more common in advanced disease.

The functional limitation from breathlessness due to COPD can be quantified easily in clinical practice[25] (see **Box 4**).

Box 4: Medical Research Council grading of functional limitation due to dyspnoea[25]

Grade	Symptom complex
1	"I only get breathless with strenuous exercise".
2	"I get short of breath when hurrying on the level or walking up a slight hill".
3	"I walk slower than most people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level".
4	"I stop for breath after walking about 100 yards or after a few minutes on the level".
5	"I am too breathless to leave the house" or "I am breathless when dressing".

C2.2 Physical examination

The sensitivity of physical examination for detecting mild to moderate COPD is poor.[26] Wheezing is not an indicator of severity of disease and is often absent in stable, severe COPD. In more advanced disease, physical features commonly found are hyperinflation of the chest, reduced chest expansion, hyperresonance to percussion, soft breath sounds and a prolonged expiratory phase. Right heart failure may complicate severe disease.

During an acute exacerbation, tachypnoea, tachycardia, use of accessory muscles, tracheal tug and cyanosis are common.

The presence and severity of airflow limitation are impossible to determine by clinical signs.[26] Objective measurements such as spirometry are essential. Peak expiratory flow (PEF) is not a sensitive measure of airway function in COPD patients, as it is effort dependent and has a wide range of normal values.[27]

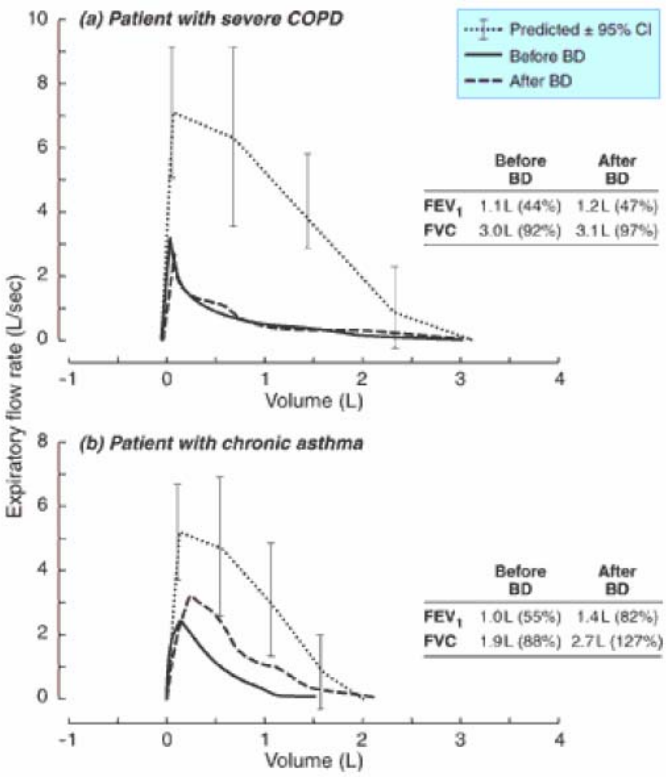
C2.3 Spirometry

> The diagnosis of COPD rests on the demonstration of airflow limitation which is not fully reversible[28] [evidence level II]

Because COPD is defined by a post-bronchodilator FEV_1/FVC ratio < 0.7, spirometry is essential for its diagnosis (see **Box 5**). Most spirometers provide predicted ("normal") values obtained from healthy population studies, and derived from formulas based on height, age, sex and ethnicity.

Airflow limitation is not fully-reversible when, after administration of bronchodilator medication, the ratio of FEV_1 to forced vital capacity (FVC) is <70% and the FEV_1 is <80% of the predicted value. The ratio of FEV_1 to vital capacity (VC) is a sensitive indicator for mild COPD.

Box 5: Maximal expiratory flow-volume curves in severe chronic obstructive pulmonary disease (COPD) and chronic asthma



The patient with COPD has reduced peak expiratory flow, and severely decreased flows at 25%, 50% and 75% of vital capacity compared with the normal range (vertical bars), and shows minimal response to bronchodilator (BD). By comparison, the patient with chronic asthma shows incomplete, but substantial, reversibility of expiratory flow limitation across the range of vital capacity. After BD the forced expiratory volume in one second (FEV_1) was within the normal range (82% predicted). Absolute and per cent predicted values for FEV_1 and forced vital capacity (FVC) before and after BD are shown for each patient.

A detailed systematic review states that spirometry, in addition to clinical examination, improves the diagnostic accuracy of COPD compared to clinical examination alone reinforcing the importance of spirometry[29] (evidence level I). More studies are required to define any benefit from the use of spirometry for case finding in COPD, and to evaluate the effects of spirometric results on smoking cessation.

The spirometric tests require high levels of patient effort and cooperation, and there are important quality criteria that should be met in conducting spirometry.[30]

Indications for spirometry include:

- breathlessness that seems inappropriate;
- chronic (daily for two months) or intermittent, unusual cough;
- frequent or unusual sputum production;
- relapsing acute infective bronchitis; and
- risk factors such as exposure to tobacco smoke, occupational dusts and chemicals, and a strong family history of COPD.

C2.4 Flow volume tests

Electronic spirometers allow for the simultaneous measurement of flow and volume during maximal expiration. Reduced expiratory flows at mid and low lung volumes are the earliest indicators of airflow limitation in COPD and may be abnormal even when FEV_1 is within the normal range (>80%).

C3. Assessing the severity of COPD

Spirometry is the most reproducible, standardised and objective way of measuring airflow limitation, and FEV_1 is the variable most closely associated with prognosis.[14] The grades of severity according to FEV_1 and the likely symptoms and complications are shown in Box 6. However, it should be noted that patients with an FEV_1 >80% predicted, although within the normal range, may have airflow limitation (FEV_1/FVC ratio <70%).

Box 6: Classification of severity of chronic obstructive pulmonary disease (COPD)[7]

	COPD severity		
Factor	**Mild**	**Moderate**	**Severe**
Spirometry findings postbronchodilator FEV_1	60%80% predicted	40%59% predicted	<40% predicted
Functional assessment (activities of daily living)	Few symptoms No effect on daily activities Breathless on moderate exertion	Increasing dyspnoea Breathless on the flat Increasing limitation of daily activities	Dyspnoea on minimal exertion Daily activities severely curtailed
Complications	No	Exclude complications; consider sleep apnoea if there is pulmonary hypertension	Severe hypoxaemia (Pao2 <60mmHg, or 8kPa) Hypercapnia (Paco2 >45mmHg, or 6kPa) Pulmonary hypertension Heart failure Polycythaemia

FEV_1=forced expiratory volume in one second. PaO_2=partial pressure of oxygen, arterial. Paco2=partial pressure of carbon dioxide, arterial.

C4. Assessing acute response to bronchodilators

The response to bronchodilators is determined to:

- assign a level of severity of airflow obstruction (post- bronchodilator); and
- help confirm or exclude asthma.

The details for this assessment are outlined in **Box 7**.

The change in FEV_1 after an acute bronchodilator reversibility test indicates the degree of reversibility of airflow limitation. This is often expressed as a percentage of the baseline measurement (eg, 12% increase). An increase in FEV_1 of more than 12% and 200mL is greater than average day-to-day variability and is unlikely to occur by chance.[31],[32] However, this degree of reversibility is not diagnostic of asthma and is frequently seen in patients with COPD (eg, the FEV_1 increases from 0.8L to 1.0L when the predicted value is, say, 3.5L). The diagnosis of asthma relies on an appropriate history and complete, or at least substantial, reversibility of airflow limitation (see also below).

Box 7: Assessment of acute response to inhaled beta-agonist at diagnosis

Preparation

Patients should be clinically stable and free of respiratory infection.

Withhold inhaled short-acting bronchodilators in the previous six hours, long-acting beta-agonists in the previous 12 hours, or sustained-release theophyllines in the previous 24 hours.

Spirometry

Measure baseline spirometry (pre-bronchodilator). An FEV_1 <80% predicted and FEV_1/FVC ratio <0.70 shows airflow limitation.

Give the bronchodilator by metered dose inhaler (MDI) through a spacer device or by nebuliser.

Give short-acting beta-agonist, at a dose selected to be high on the dose–response curve (eg, 200–400mcg salbutamol from MDI and spacer).

Repeat spirometry 15–30 minutes after bronchodilator is given and calculate reversibility.

FEV_1=forced expiratory flow in one second.
FVC=forced vital capacity.

C4.1 Confirm or exclude asthma

If airflow limitation is fully or substantially reversible, the patient should be treated as for asthma

Asthma and COPD are usually easy to differentiate. Asthma usually runs a more variable course and dates back to a younger age. Atopy is more common and the smoking history is often relatively light (eg, less than 15 pack-years). Airflow limitation in asthma is substantially, if not completely, reversible, either spontaneously or in response to treatment. By contrast, COPD tends to be progressive, with a late onset of symptoms and a moderately heavy smoking history (usually >15 pack-years) and the airflow obstruction is not completely reversible.

However, there are some patients in whom it is difficult to distinguish between asthma and COPD as the primary cause of their chronic airflow limitation. Long-standing or poorly controlled asthma can lead to chronic, irreversible airway narrowing even in non-smokers, thought to be due to airway remodelling resulting from uncontrolled airway wall inflammation with release of cytokines and mediators.

Furthermore, asthma and COPD are both common conditions, and it must be expected that the two can coexist as least as often as the background prevalence of asthma in adults.

C5. Specialist referral

Confirmation of the diagnosis of COPD and differentiation from chronic asthma, other airway diseases or occupational exposures that may cause airway narrowing or hyper-responsiveness, or both, often requires specialised knowledge and investigations. Indications for which consultation with a respiratory medicine specialist is recommended are shown in **Box 8**.

Box 8: Indication for referral to specialist respiratory outpatient services

Reason	Purpose
Diagnostic uncertainty and exclusion of asthma	Establish diagnosis and optimise treatment. Check degree of reversibility of airflow Obstruction
Unusual symptoms such as haemoptysis	Investigate cause including exclusion of Malignancy
Rapid decline in FEV_1	Optimise management
Moderate or severe COPD	Optimise management
Onset of cor pulmonale	Confirm diagnosis and optimise treatment
Assessment of home oxygen therapy: ambulatory or long-term oxygen therapy	Optimise management, measure blood gases and prescribe oxygen therapy
Assessing the need for pulmonary rehabilitation	Optimise treatment and refer to specialist or community-based rehabilitation service
Bullous lung disease	Confirm diagnosis and refer to medical or surgical units for bullectomy
COPD <40 years of age	Establish diagnosis and exclude alpha1-antitrypsin deficiency
Assessment for lung transplantation or lung volume reduction surgery	Identify criteria for referral to transplant Centres
Frequent chest infections	Rule out co-existing bronchiectasis
Dysfunctional breathing	Establish diagnosis and refer for pharmacological and non-pharmacological management
FEV_1, forced expiratory volume in 1s; COPD, chronic obstructive pulmonary disease. Table adapted from British Thoracic Society Statement[33]	

C5.1 Complex lung function tests

Measurement of airways resistance, static lung volumes and diffusing capacity of lungs for carbon monoxide assists in the assessment of patients with more complex respiratory disorders. Inspiratory capacity (IC) indicates the degree of hyperinflation, which relates to a patient's level of dyspnoea and their exercise tolerance, and is a better predictor of mortality than spirometry. It is therefore finding increased utility for assessing people with COPD as well as response to therapy in clinical research. More specialised measures, including forced oscillometry, have not yet found clinical application despite their relative ease of use.

C5.2 Exercise testing

Cardiopulmonary exercise tests may be useful to differentiate between breathlessness resulting from cardiac or respiratory disease, and may help to identify other causes of exercise limitation (eg, hyperventilation, musculoskeletal disorder). Exercise prescription and monitoring of outcomes from drug or rehabilitation therapies are additional uses for these tests. Walking tests (6-minute walking distance and shuttle tests) are also useful, and can indicate whether exercise oxygen desaturation is occurring.

C.5.3 Sleep studies

Specialist referral is recommended for COPD patients suspected of having a coexistent sleep disorder or with hypercapnia or pulmonary hypertension in the absence of daytime hypoxaemia, right heart failure or polycythaemia. Overnight pulse oximetry may be used to assess a need for overnight domiciliary oxygen therapy, and may be indicated in patients receiving long-term domiciliary oxygen therapy to assess whether hypoxaemia has been adequately corrected.

C5.4 Chest x-rays

A plain posteroanterior and lateral chest x-ray helps to exclude other conditions such as lung cancer. The chest x- ray is not sensitive in the diagnosis of COPD, and will not exclude a small carcinoma (<1cm).

C5.5 High resolution computed tomography

High resolution computed tomography (HRCT) scanning gives precise images of the lung parenchyma and mediastinal structures. The presence of emphysema and the size and number of bullae can be determined. This is necessary if bullectomy or lung reduction surgery is being contemplated. HRCT is also appropriate for detecting bronchiectasis. Vertical reconstructions can provide a virtual bronchogram.

Helical computed tomography (CT) scans with intravenous contrast should be used in other circumstances, such as for investigating and staging lung cancer.

CT pulmonary angiograms are useful for investigating possible pulmonary embolism, especially when the chest x- ray is abnormal.

C5.6 Ventilation and perfusion scans

The ventilation and perfusion (V/Q) scan may be difficult to interpret in COPD patients, because regional lung ventilation may be compromised leading to matched defects. If pulmonary emboli are suspected, a CT pulmonary angiogram may be more useful. Quantitative regional V/Q scans are helpful in assessing whether patients are suitable for lung resection and lung volume reduction surgery.

C5.7 Transcutaneous oxygen saturation

Oximeters have an accuracy of plus or minus 2%, which is satisfactory for routine clinical purposes. They are more useful for monitoring trends than in single measurements. Oximetry does not provide any information about carbon dioxide status and is inaccurate in the presence of poor peripheral circulation (eg, cold extremities, cardiac failure).

C5.8 Arterial blood gas measurement

Arterial blood gas analysis should be considered in all patients with severe disease, those being considered for domiciliary oxygen therapy (eg, whose FEV_1 is <40% predicted or <1L, whose oxygen saturation as measured by pulse oximetry [Spo2] is <92%), those with pulmonary hypertension, and those with breathlessness out of proportion to their clinical status). Respiratory failure is defined as a Pao2 <60mmHg (8kPa) or Paco2 >50mmHg (6.7kPa). The latter is termed ‘ventilatory failure’ and is accompanied by either compensated (chronic) or uncompensated (acute) acidosis. Acute respiratory acidosis indicates a need for assisted ventilation.

C5.9 Sputum examination

Routine sputum culture in clinically stable patients with COPD is unhelpful and unnecessary. Sputum culture is recommended when an infection is not responding to antibiotic therapy or when a resistant organism is suspected.

C5.10 Haematology and biochemistry

Polycythaemia should be confirmed as being secondary to COPD by blood gas measurement that demonstrates hypoxaemia. The possibility of sleep apnoea or hypoventilation should be considered if polycythaemia is present but oxygen desaturation or hypoxaemia on arterial blood gas tests are absent when the patient is awake. Hyperthyroidism and acidosis are associated with breathlessness. Hyperventilation states are associated with respiratory alkalosis. Hypothyroidism aggravates obstructive sleep apnoea.

The prevalence of severe homozygous (ZZ) alpha1 antitrypsin deficiency has been estimated at between 1/4,348 and 1/5,139 in European populations[34]. Although 75 to 85% of such individuals will develop emphysema, tobacco smoking is still the most important risk factor for COPD even in this group. Targeted screening suggests between 1.0 – 4.5% of patients with COPD have underlying severe a_1 AT deficiency[35]. The index of suspicion should be high in younger Caucasian patients with predominantly basal disease and a family history. The diagnosis can be made by measuring serum levels of alpha1 antitrypsin and if reduced, genotyping should be performed.

C5.11 Electrocardiography and echocardiography

Electrocardiography is indicated to confirm arrythmias suspected on clinical grounds. Multifocal atrial tachycardia is a rare arrhythmia (prevalence < 0.32% of hospitalised patients) but over half the cases reported in the literature had underlying COPD.[36] Atrial fibrillation commonly develops when pulmonary artery pressure rises, leading to increased right atrial pressure.

Echocardiography is useful if cor pulmonale is suspected, when breathlessness is out of proportion to the degree of respiratory impairment or when ischaemic heart disease, pulmonary embolus or left heart failure are suspected. Patients with COPD may have poor quality images on transthoracic examination and transoesophageal echocardiography may be frequently needed.

Consider COPD in patients with other smoking-related diseases[37],[38],[39] [evidence level I]

Patients with COPD are prone to other conditions associated with cigarette smoking, including accelerated cardiovascular, cerebrovascular and peripheral vascular disease, and oropharyngeal, laryngeal and lung carcinoma. Conversely, there is a high prevalence of COPD among patients with ischaemic heart disease, peripheral vascular disease and cerebrovascular disease and smoking-related carcinomas.[37] These patients should be screened for symptoms of COPD, and spirometry should be performed.

C5.12 Trials of Therapy

The evidence supporting the utility of specific diagnostic tests in COPD is typically not of the same strength as that for specific therapies reviewed in subsequent sections. The evidence base for tests used in the diagnosis and monitoring of a number of respiratory diseases at one specialist referral clinic was reviewed by Borrill et al.[40] They were unable to identify any evidence to support the use of peak flow charts to assess treatment with inhaled steroids in patients with pre-diagnosed COPD. Studies were found that did not support the diagnostic use of trials of therapy with inhaled or oral steroids in COPD. There was no evidence to support the diagnostic use of trials of therapy with short or long acting bronchodilators or oral theophyllines in COPD. However, it should be remembered that absence of evidence is not the same as evidence of absence of utility.

O: Optimise function

The principal goals of therapy are to stop smoking, to optimise function through symptom relief with medications and pulmonary rehabilitation, and to prevent or treat aggravating factors and complications.

Confirm Goals of Care

Addressing the goals of care is one of the most complex clinical issues in the management of COPD.

- **Active therapy:** In the early stages of the disease the goals of care must be to delay the progress of the disease by aggressive treatment of acute exacerbations in order that patient function is optimised and their health is maintained. In this setting management of disease may provide the best symptom control. Should the goal of health maintenance not result in adequate symptom control then a palliative approach may also be required to augment active therapy. During this period of the patient's disease trajectory any change in therapy should be seen as an opportunity to review the goals of care in general terms with the patient.
- **Active therapy with treatment limitations:** The transition phase of health maintenance to functional deterioration despite maximal therapy is difficult to define. The burden of disease and care fluctuates and it may be appropriate to encourage discussion about long term goals prognosis and attitudes to future treatment and care plans can be encouraged. The initiation of long term oxygen therapy and functional deterioration have been found to be an important point at which patient's may be receptive to reviewing the goals of care, end of life care and treatment limitations.
- **Palliative and supportive care:** Functional deterioration in the presence of optimum treatment requires a reappraisal of the goals of care. Each exacerbation may be reversible until there is a suboptimal or no response to treatment. At this point the patient may enter their terminal phase and the goals of care may change rapidly to palliation with treatment limitations or palliation alone with withdrawal of active therapy. In this setting (unstable, deterioration or terminal care) the goals of care need to shift from active therapy to one of palliation. Should the patient recover despite a palliative approach then the goals of care may continue to be active management in preparation for the next crisis. A review of symptom management, end of life care issues, and advanced directives should take place to prepare for the next crisis.
- **Terminal care:** Terminal care plans may be appropriate for patients who elect to avoid active management. These plans need to be communicated to all services involved in the care of the patient so that there is a continuity of care. In this situation the goals of care should be clearly communicated and the advanced directive, terminal care plan and the location of care documented. Patients may elect to be treated palliatively in their terminal phase† by their respiratory physician owing to their long-standing relationship with the clinician. Terminal care does not always require specialist palliative care unless there are problems with symptom control or other complex needs. Hospice or specialist consultations should be available to patients should they be required.

Terminal Phase is characterised by the following criteria:

1. Profound weakness
2. Essentially bedbound (ECOG 4)
3. Drowsy for extended periods
4. Disorientated to time with poor attention span
5. Disinterested in food or fluids
6. Difficulty swallowing medications

O1. Inhaled bronchodilators

Inhaled bronchodilators provide symptom relief and may increase exercise capacity[41-48] [evidence level I]

O1.1 Short-acting bronchodilators

O1.1.1 Short-acting beta-agonists

Regular short-acting beta-agonists improve lung function and daily breathlessness scores. A systematic review of randomised controlled trials[49] found a significant increase in post-bronchodilator spirometry when compared to placebo; weighted mean difference = 140mls (95% CI 40 to 250) for FEV_1 and 300mls (95% CI 20 to 580) for FVC. There were also improvements in post-bronchodilator morning and evening PEF: weighted mean difference = 29.17 l/min (95% CI 0.25 to 58.09) for morning and 36.75 l/min (95% CI 2.57 to 70.94) for evening measurements. The relative risk of dropping out of the study was 0.49 (95% CI 0.33 to 0.73), giving a number needed to treat of 5 (95% CI 4 to 10) to prevent one treatment failure. There was no significant benefit on functional capacity, measured by walking tests, or symptoms other than breathlessness, although one randomised controlled trial has found a significant improvement in six-minute walking distance and quality of life.[46] Short-acting beta-agonists are now usually prescribed for use as "rescue" medication, i.e. for relief of breathlessness, rather than for regular use.

O1.1.2 Short-acting anticholinergics

The duration of action of short-acting anticholinergics is greater than short-acting beta-agonists. A systematic review of randomised controlled trials comparing ipratropium bromide alone, or in combination with short-acting beta-agonists, against short-acting beta-agonists alone found significant benefits for regimens containing ipratropium bromide.[50] Ipratropium bromide improved spirometry over short-acting beta-agonists alone, weighted mean difference = 30mls (95% CI 0 to 60) for FEV_1 and 70mls (95% CI 10 to 140) for FVC. Ipratropium bromide improved quality of life, with a statistically significant improvement in all domains of the Chronic Respiratory Disease Questionnaire. These benefits occurred with fewer adverse drug effects, Number Needed to Harm (NNH) = 32 (95% CI 20 to 316). There was a lesser need to add or increase the dose of oral glucocorticoids for participants receiving ipratropium bromide , with 15 (95% CI 12 – 28) people requiring treatment with ipratropium bromide to prevent one receiving additional oral glucocorticoids.

Ipratropium bromide is associated with an increased risk of adverse cardiovascular effects[51, 52]. A nested case-control study[51] [evidence level III-2] found an increased risk of cardiovascular death associated with the prescription of ipratropium, OR 1.34 (95% CI 1.22 to 1.47). A meta-analysis of randomised controlled trials[52] found an increased risk for a combined cardiovascular endpoint of cardiovascular death, myocardial infarction and stroke, estimated NNH for cardiovascular death 40 (95% CI 18 to 185) per year. The consistent finding across these studies suggests the cardiovascular adverse effects are likely to be real [evidence level I].

O1.1.3 Short-acting bronchodilator combinations

For combination therapy with ipratropium bromide and short-acting beta-agonists, there was no significant difference in pre-drug spirometry compared to ipratropium bromide alone.[50] There was a significant benefit for the combination in post-drug spirometry measurements; weighted mean difference = 70 mls (95% CI 50 to 90) for FEV_1 and 120mls (95% CI 80 to 160) for FVC. There was no significant difference between interventions for quality of life or adverse drug effects, but combination treatment decreased the need to add or increase oral glucocorticoids compared to ipratropium bromide alone, Number Needed to Treat = 20 (95% CI 12 to 108).

In summary, short-acting bronchodilators, either beta-agonists or ipratropium bromide, significantly increase lung function measurements in COPD. Ipratropium bromide has a significantly greater effect on lung function compared to beta-agonists alone; in addition to improving quality of life and decreasing need for oral glucocorticoid treatment. These benefits occurred with a decreased risk of adverse drug effects. Combining two classes of bronchodilator may provide added benefits without compounding adverse effects.

Box 9: Initial treatment with short-acting bronchodilators*

Severity	FEV_1	Suggested treatment
Mild COPD	60%80%	Intermittent bronchodilator salbutamol (200mcg) or ipratropium bromide (40mcg) as needed before exercise
Moderate COPD	40%59%	Intermittent or regular bronchodilator salbutamol (200-400mcg four times daily) or ipratropium bromide (40mcg four times daily) Combination bronchodilators may be considered
Severe COPD	<40%	Regular combination bronchodilator salbutamol (200-400mcg four times daily) and ipratropium bromide (40-80mcg four times daily)

*Modified from GOLD.[7] FEV_1=forced expiratory volume in one second. COPD=chronic obstructive pulmonary disease.

O1.2 Long-acting bronchodilators

Long-acting bronchodilators produce significant improvements in lung function, symptoms and quality of life, as well as decreasing exacerbations. These benefits come at a cost of increased adverse effects, which are generally of mild to moderate severity.

O1.2.1 Long-acting anticholinergics

Tiotropium is a long-acting anticholinergic agent with duration of action of over 24 hours and is used once daily. Two systematic reviews of randomised controlled trials of its clinical effects have been published.[53],[54] These had differing inclusion criteria, particularly the duration of treatment, and consequently slightly different results. Compared to placebo, the reviews found tiotropium produced a significant increase in FEV_1 in the order of 130mls and improved quality of life, decreasing the mean St George's Respiratory Questionnaire by about 3 units. The number of patients needed to treat (NNT) with tiotropium for one year were 14 (95% CI 11 to 22) to prevent one exacerbation and 30 (95% CI 22 to 61) to prevent one hospitalisation compared to placebo or ipratropium.

The beneficial effects come at a cost of increased adverse drug effects. A pooled study of placebo controlled trials[55] found an increased risk of dry mouth (RR=3.60; 95% CI, 2.56 to 5.05) and urinary retention (RR=10.93, 95% CI, 1.26 to 94.88), although the latter occurred infrequently.[55] These effects have been confirmed in a large four-year randomised-controlled trial[56] which found no increase in death from any cause, RR 0.89 (95% CI 0.79 to 1.02) [evidence level II]. There was a decreased rate of serious adverse cardiac events in patients randomised to tiotropium compared to placebo.

O1.2.2 Long-acting beta-agonists

Long-acting beta-agonists (eg salmeterol, eformoterol) cause prolonged bronchodilatation, for at least 12 hours, and can thus be administered twice daily. A systematic review of randomised controlled trials[57] found that compared to placebo, long-acting beta-agonists used for at least four weeks produce statistically significant benefits in lung function, quality of life, use of 'reliever' short-acting bronchodilators and acute exacerbations. This review compared different drugs and doses independently, the commonest being salmeterol 50 mcg daily which involved up to 3363 participants. It would be necessary to treat 24 (95% CI 14 to 98) patients with salmeterol to prevent one exacerbation.

The review did not find evidence that higher doses of salmeterol were more beneficial than 50mcg/day. Fewer studies of the effect of eformoterol were included and they were not combined in a meta-analysis, but some benefits similar to those of salmeterol were seen for a range of outcomes across a range of doses. Adverse drug effects were not reported.

O1.2.3 Long-acting bronchodilator combinations

The efficacy of long-acting beta-agonists compared to ipratropium bromide, alone or in combination, have also been combined in a systematic review.[50] Comparisons of monotherapy found a greater increase in FEV_1, weighted mean difference = 60 mls (95% CI 0 to 110), and morning PEF, weighted mean difference = 10.96 l/min (95% CI 5.83 to 16.09) for salmeterol over ipratropium bromide. There were no significant differences between interventions for quality of life, functional capacity, symptoms, acute exacerbations or adverse events. Comparisons of the combination of ipratropium bromide and salmeterol with ipratropium bromide alone showed varying effects on lung function and symptoms, but a small, significant reduction in reliever use; weighted mean difference = -0.67 puffs/day (95% CI -1.11 to -0.23).

O1.3 Assessment of response and continuation of bronchodilator therapy

In some patients a response to bronchodilator therapy may require treatment for up to two months. Symptomatic and functional benefits can often be demonstrated in the absence of an increase in FEV_1. Other objective measurements, such as an increase in exercise capacity (e.g., six-minute walk distance) or an increased inspiratory reserve capacity, may be useful indicators of physiological improvement.

Subjective measurements, such as quality of life, breathlessness and functional limitation (e.g., MRC Dyspnoea Scale), can determine the patient's perception of benefit.

If there is no improvement:

- check inhaler technique;
- consider psychosocial issues and deconditioning; and
- exclude other causes of exercise impairment (consider specialist referral or a cardiopulmonary exercise test).

O2. Oral bronchodilators

O2.1 Methylxanthines

Theophylline has a modest effect on FEV_1 and FVC[58] and slightly improves arterial blood gas tensions in moderate to severe COPD. However, theophyllines have gone out of favour in many countries because of their narrow therapeutic index and potential for significant side effects.[59],[60] Some patients with disabling breathlessness may, however, derive benefit from their use.[61-63] Theophyllines may have an anti-inflammatory effect or reduce muscle fatigue.[64],[65] Recent studies have suggested lower dose preparations than had previously been used (achieving plasma levels of 5-10mg/L) may have anti-inflammatory or immuno-modulatory effects.[66, 67] A randomised placebo controlled trial in China demonstrated that doses of 100mg twice daily reduced exacerbations compared with placebo.[68] Evidence supports only the slow-release formulation. Theophylline is effective in COPD but due to its potential toxicity (the most common adverse reactions being gastric irritation, nausea, vomiting, anorexia, epigastric pain, reactivation of peptic ulcer, gastro-oesophageal reflux, haematemesis, tachycardia, palpitations, headache, CNS stimulation, reflex hyperexcitability, insomnia and tremor[69]), inhaled bronchodilators are preferred when available.[11] Theophylline has an extensive drug interaction profile that may present potential adverse effects in patients on some multi-medication regimens. The macrolide antibiotics, particularly erythromycin and quinolone antibiotics when used concurrently can lead to increased theophylline plasma concentrations and reduced antibiotic concentrations.

O2.2 Phosphodiesterase type-4 inhibitors

Inhibitors of phosphodiesterase type-4 (PDE-4) act by increasing intracellular concentrations of cyclic adenosine monophosphate and causing a range of anti-inflammatory effects.

Two drugs, cilomilast and roflumilast, have been developed, but neither has been approved for use in Australia or New Zealand at this time. Placebo controlled studies up to six months duration[70],[71] have found that PDE-4 inhibitors attenuate decline in lung function and quality of life, and decrease acute exacerbations when compared to placebo [evidence level II].

PDE-4 inhibitors significantly increase the FEV_1, by an order of 40 - 100ml, compared to placebo. They improve quality of life, measured by the SGRQ total score, by 1.6 - 4.1 units compared to placebo, but the changes did not reach statistical significance in all studies. PDE-4 inhibitors significantly reduced acute exacerbations, whether measured by the mean number of exacerbations or exacerbation-free survival. Drug related adverse effects mainly affected the gastrointestinal system; diarrhoea, abdominal pain, nausea and vomiting, and were approximately twice as common in subjects taking PDE-4 inhibitors as in those taking placebo.

PDE-4 inhibitors are promising candidates for the treatment of chronic obstructive pulmonary disease. Further research is required to determine their long-term impact and role when used with other treatments including glucocorticoids and long-acting bronchodilators.

O3. Glucocorticoids

Long term use of systemic glucocorticoids is not recommended[72-76][evidence level I]

Indeed, caution in the long term use of systemic glucocorticoids is necessary because of limited efficacy and potential toxicity in elderly patients.

O3.1 Oral glucocorticoids

Some patients with stable COPD show a significant response to oral glucocorticoids (on spirometry or functional assessment). Therefore, a short course (two weeks) of prednisolone (20–50mg daily) may be tried with appropriate monitoring. Short courses of oral glucocorticoids (<14 days) do not require tapering. A negative bronchodilator response does not predict a negative steroid response.[7],[77] If there is a response to oral steroids, continued treatment with inhaled glucocorticoids is indicated, but these may fail to maintain the response.[77],[78] Patients who have a negligible response to glucocorticoids should not use them.

O3.2 Inhaled glucocorticoids

Inhaled glucocorticoids should be considered in patients with severe COPD and frequent exacerbations [evidence level 2]

Acute exacerbations have a detrimental effect on quality of life, and patients with severe disease and frequent exacerbations have an accelerated decline in their quality of life.[79] A number of randomised controlled trials of high dose glucocorticoids have been published and these have been combined in a systematic review[80], mainly involving subjects without bronchodilator reversibility or bronchial hyper-responsiveness. Unfortunately, this review does not include all the data from a recently published large randomised controlled trial involving 6000 participants.[81]

Inhaled glucocorticoids decrease the exacerbation rate compared to placebo in studies longer than a year, weighted mean difference -0.26 exacerbations per participant, per year (95% CI -0.37 to -0.14, 2586 participants). They also show the rate of decline in quality of life, the weighted mean difference in rate of change for the St George's Respiratory Questionnaire was -1.22 units/year (95% CI-1.83 to -0.60, 2507 participants).

Inhaled glucocorticoids do not improve mortality. Pooled results from nine studies involving 8,390 participants found an odds ratio of death of 0.98 (95% CI 0.83 to 1.16). The effect of inhaled glucocorticoids on the decline in lung function remains unclear. Pooled results from studies of two years duration or longer, found no significant difference in the rate of decline in post-bronchodilator FEV_1[80], weighted mean difference = 5.8mls/year (95% CI -0.28 to 11.88, 2,333 participants), although this analysis did not include the TORCH study[81], which did find a significant benefit (weighted mean difference in FEV_1 over three years = 47mls, 95% CI 31 to 64 mls, 2,617 participants).

Patients with clinically significant acute bronchodilator reversibility may benefit from long-term inhaled glucocorticoid therapy. Long term inhaled therapy with glucocorticoids is also indicated in patients with COPD who have significant reversibility of airway function after a more prolonged trial of bronchodilators or glucocorticoids, as these patients probably have mixed asthma and COPD.[77, 78, 82]

In a large RCT in patients with milder COPD, medium-dose budesonide had no significant impact.[82] Some systemic absorption may occur, so the modest benefits of inhaled glucocorticoids must be weighed against the potential risks of local oropharyngeal adverse effects, easy bruising, cataract formation and possible contribution to osteoporosis. Local adverse effects include oral candidiasis with a NNH of 38 (95% CI 23-71) and hoarseness or dysphonia with a NNH of 35 (95% CI 20-79). Pooling of studies longer than six months duration found an odds ratio of 2.49 (95% CI 1.78 to 3.49, 4380 participants) for candidiasis and 1.95 (95% CI 1.41 to 2.70) for hoarseness or dysphonia.

The response should be assessed with spirometry and measures of performance status, quality of life or both. They should be trialled for three to six months in patients with moderate to severe COPD, and continued if there is objective benefit. Withdrawal of inhaled steroids may be associated with a decline of FEV_1, increased symptoms and a greater rate of mild exacerbations[83] [evidence level II]. However, it is not clear whether this applies to patients who have not responded to oral steroids.

O4. Inhaled combination therapy

O4.1 Inhaled glucocorticoids and long-acting beta-agonists in combination

A systematic review of six randomised controlled trials involving 4,118 participants of combined glucocorticoid steroids and long-acting beta2-agonists in one inhaler[84] for COPD reached the following conclusion: Compared with placebo, combination therapy led to clinically meaningful differences in quality of life, symptoms and exacerbations. There was also a statistically significant difference in lung function. However, there were conflicting results when the different combination therapies were compared with the mono-components alone. There was a statistically significant reduction in exacerbation rate for budesonide and formoterol, or fluticasone and salmeterol when compared to placebo, rate ratio 0.76 (95% CI 0.68, 0.84). There was also a statistically significant reduction in exacerbation rate for combination therapy versus long-acting beta2-agonists, rate ratio 0.85 (0.77, 0.95) but not for combination therapy compared to inhaled glucocorticoids. There was a significant difference in the change from baseline in pre-dose FEV_1, weighted mean difference 160mls (95% CI 120-200, 697 participants). There were conflicting results for quality of life and symptom scores for both treatment comparisons and combinations (budesonide and formoterol, or fluticasone and salmeterol). Possible explanations for these conflicts include study design and differential drop outs for interventions between studies. Although there was no significant difference (or any adverse event), oral candidiasis was significantly more common with combination therapy, NNH 16 (8-36), 1436 participants). More recent data from Calverley et al[81][evidence level II], and a study by Kardos et al[85] [evidence level II] confirm that combined therapy with salmeterol and fluticasone (in one inhaler) is superior to placebo or monotherapy with either drug alone for reducing exacerbations and improving health-related quality of life. These results were noted in patients with both moderate and severe COPD (FEV_1<60%) in the Calverley study, and in patients with severe COPD in the study by Kardos et al (FEV_1 <50%). In addition, in the Calverley study, combination therapy, compared with placebo, was associated with a 2.6% reduction in all cause mortality over three years (although this finding was of borderline statistical significance, p=0.052), NNT=39. In both studies, however, an increased rate of pneumonia (defined on clinical grounds) was noted in the inhaled glucocorticoid arms. The pneumonia rates in the Calverley study were: 19.6% in the combination group, 18.3% in the fluticasone alone group and 12.3% in the placebo group (p<0.001 for both comparisons). These results contrast with the reductions in exacerbation rates induced by these drugs. A nested case control study from Canada[86] [evidence level III-2] using databases linking hospitalisations and drug dispensing information also found an increased risk of pneumonia and hospitalisation from pneumonia in those prescribed and dispensed inhaled glucocorticoids and that this appeared dose-related. Further prospective studies using objective pneumonia definitions may clarify the situation. Meantime, increased vigilance and patient education about prompt treatment of infections would seem prudent.

O4.2 Inhaled glucocorticoids and long-acting beta-agonists and long-acting anticholinergics in combination

A recent study comparing tiotropium and combination therapy with fluticasone/ salmeterol (500/50bd) in a double-blind, double dummy randomised controlled trial over two years[87] found no difference in exacerbation rate between the groups (the primary aim of the study). The probability of withdrawing from the study was higher in the tiotropium group. The combination therapy group achieved a small, statistically significant benefit in quality of life (as well as the unexpected benefit of fewer deaths) [evidence level II].

In clinical practice, many patients with COPD receive multiple inhaled medications aiming to optimize their lung function and improve symptoms. In order to determine whether combining therapies with different pharmacological properties provides added benefits, Aaron et al[88] [evidence level II] randomised patients with moderate to severe COPD to receive placebo, salmeterol or combined salmeterol/ fluticasone in addition to tiotropium. Although combined “triple” therapy did not reduce the proportion of patients suffering at least one exacerbation during the one year of the study (the primary study endpoint), those in this group did experience fewer hospitalisations for COPD and for all causes than the tiotropium plus placebo group. The patients receiving “triple” therapy also experienced a clinically significant improvement in their quality of life compared with the tiotropium plus placebo group [evidence level II].

O5. Inhaler technique

Inhaler devices must be explained and demonstrated for patients to achieve optimal benefit. It is necessary to check regularly that the patient has the correct inhaler technique. Elderly and frail patients, especially those with cognitive deficits, may have difficulty with some devices. The cost of inhaler devices varies between products. As there are no differences in patient outcomes for the different devices, the cheapest device the patient can use adequately should be prescribed as first line treatment.[89] The range of devices currently available, the products and dosage, as well as their advantages or disadvantages, are listed in Appendix 2.

O6. Non-pharmacological interventions

O6.1 Physical activity

Many people with COPD are markedly inactive in daily life.[90] Regular physical activity is recommended for all individuals with COPD and has been shown to reduce the risk of COPD admissions and mortality (evidence level III-2). This recommendation is based on a population-based sample of 2,386 individuals with COPD who were followed for a mean of 12 years. Those who performed some level of regular physical activity had a significantly lower risk of COPD admissions or mortality than sedentary individuals.[91]

O6.2 Exercise training

Exercise training is considered to be the essential component of pulmonary rehabilitation.[92],[93], Numerous randomised controlled trials in patients with moderate to severe COPD have shown decreased symptoms (breathlessness and fatigue),increased exercise endurance and improved, health-related quality of life, emotional function and the patients' self-control over their condition following exercise training alone[94] [evidence level I]. Improvements in muscle strength and self-efficacy have also been reported.[93] Exercise training also improves exercise tolerance in individuals with mild disease.[95]

Inspiratory muscle training (IMT), performed in isolation using a threshold loading device or target-flow resistive device, has been demonstrated to increase inspiratory muscle strength and endurance and reduce dyspnoea in patients with COPD[96],[97] [evidence level I]. It remains unclear whether IMT combined with a program of whole-body exercise training confers additional benefits in dyspnoea, exercise capacity or health-related quality of life. in subjects with COPD.[98] At present, the evidence does not support the routine use of IMT as an essential component of pulmonary rehabilitation.[93]

Some very disabled patients are shown how to reduce unnecessary energy expenditure during activities of daily living.[92] Some patients who experience marked oxygen desaturation on exertion may benefit from ambulatory oxygen during exercise training and activities of daily living. (see **Section P11**).

Maintenance of regular physical activity is essential for continuing the benefits from the initial training program.[93] Transfer of the exercise and education components of the initial pulmonary rehabilitation program into the home setting should be emphasised in an attempt to encourage long-term adherence. Exacerbations are reported by patients with COPD to be the commonest reason for non-adherence with exercise.[99] Several strategies for maintaining regular exercise and self-management have been studied; however, there is no consensus as to the most effective strategy for maintaining the benefits of pulmonary rehabilitation.[92],[93]

O6.3 Education and self-management

There is limited evidence that education alone can improve self-management skills, mood and health-related quality of life. Education should be included with exercise training as part of a comprehensive pulmonary rehabilitation program[93][evidence level III-2]. Delivering COPD-specific information in a didactic style is unlikely to be beneficial and therefore is not recommended.[100]Providing information and tools to enhance self-management in an interactive session is more effective than didactic teaching.[101],[100]

A systematic review of self-management education for COPD[102] concluded that self-management education is associated with a significant reduction in the probability of at least one hospital admission when compared with usual care , which translates into a one-year Number Needed to Treat ranging from 10 (6 to 35) for individuals with a 51% risk of exacerbation to a Number Needed to Treat of 24 (16 to 80) for patients with a 13% risk of exacerbation. This review also showed a small but significant reduction in dyspnoea measured using the Borg 0-10 dyspnoea scale. However, the magnitude of this difference (weighted mean difference -0.53, 95% CI -0.96 to -0.10) is unlikely to be clinically significant. No significant effects were found in the number of exacerbations, emergency room visits, lung function, exercise capacity and days lost from work. Inconclusive results were observed in doctor and nurse visits, symptoms (other than dyspnoea), the use of courses of glucocorticoids and antibiotics and the use of rescue medication. However, because of the heterogeneity in interventions, study populations, follow-up time and outcome measures, data are insufficient to formulate clear recommendations regarding the format and content of self-management education programs for individuals with COPD.

The single most important intervention is assistance with smoking cessation.[7] Good nutrition; task optimisation for more severely disabled patients; access to community resources; help with control of anxiety, panic or depression; instruction on effective use of medications and therapeutic devices (including oxygen where necessary); relationships; end-of-life issues; continence; safety for flying; and other issues may be addressed.[7], [92],[103]

O6.3.1 Psychosocial support

Improved exercise tolerance, mood, self-efficacy and health-related quality of life have been reported from cognitive behavioural therapy alone[103],[104] [evidence level III-2]. Depression, anxiety and panic are frequent complications of chronic disabling breathlessness, with dependence and social isolation being common.[105, 106] General support, specific behavioural training and the use of appropriate antidepressant medications may enhance quality of life for the patient, and for the spouse or carer.

Lung support groups may provide patients and carers with emotional support, social interaction, and other social outlets, and help them gain new knowledge and coping strategies. More than 100 groups throughout Australia can be contacted via The Australian Lung Foundation's LungNet Information & Support Centre (toll-free phone number, **1800 654 301**; Internet address, http://www.lungnet.com.au). In New Zealand, contact the Asthma and Respiratory Foundation of New Zealand (phone +64 4 499 4592; Internet address, http://www.asthmanz.co.nz).

O6.4 Pulmonary rehabilitation

> Pulmonary rehabilitation reduces dyspnoea, fatigue, anxiety and depression, improves exercise capacity, emotional function and health-related quality of life and enhances patients' sense of control over their condition [evidence level I].
>
> Pulmonary rehabilitation reduces hospitalisation and has been shown to be cost-effective [evidence level II].

Pulmonary rehabilitation programs involve patient assessment, exercise training, education, nutritional intervention and psychosocial support.[92]An online toolkit is available to assist health professionals to implement a Pulmonary Rehabilitation Program. See www.pulmonaryrehab.com.au

Pulmonary rehabilitation is one of the most effective interventions in COPD[94],[93] and has been shown to reduce symptoms, disability and handicap, reduce hospitalisation[107, 108] and to improve function by:

- improving peripheral muscle function, cardiovascular fitness, muscle function and exercise endurance[93, 94, 109];
- enhancing the patient's emotional function, self-confidence and coping strategies, and improving adherence with medications;[94, 103]
- improving mood by controlling anxiety and panic, decreasing depression, and reducing social impediments[93].

Pulmonary rehabilitation should be offered to patients with moderate to severe COPD, but can be relevant for people with any long-term respiratory disorder characterised by dyspnoea.[92],[93] Exercise programs alone have clear benefits,[94] while the benefits of education or psychosocial support without exercise training are less well documented.[93],[92] Comprehensive programs incorporating all three interventions have the greatest benefits (see below).

Most research has been undertaken with hospital-based programs, but there is also evidence of benefit from rehabilitation provided to in-patients and in the community and home settings.[92],[110],[111],[93] The minimum length of an effective rehabilitation program that includes exercise training is six weeks; however, there is some evidence of dose response-effect with longer programs producing greater and more sustained benefits in exercise tolerance[93][evidence level II].

O6.5 Chest physiotherapy (Airway clearance techniques)

The aims of airway clearance techniques in patients with COPD are to assist sputum removal and improve lung ventilation in an attempt to slow the decline in lung function and relieve symptoms. Chest x-ray/ CT findings and auscultation help determine the regions of the lung to be treated. Short-acting inhaled bronchodilators prior to treatment may assist with sputum clearance in some patients.

A variety of techniques are available including conventional chest physiotherapy (defined as any combination of gravity-assisted drainage, percussion, vibrations and directed coughing), the Active Cycle of Breathing Techniques (ACBT), Positive Expiratory Pressure (PEP) therapy, oscillating devices (Flutter®, or Acapella®).

A systematic review of bronchopulmonary hygiene therapy in COPD and bronchiectasis showed a significant increase in sputum production and isotope clearance from the lung with no change in lung function or health status[112] [evidence level I]. However, the trials were all small and not generally of high quality. Further, the results could not be combined as the trials addressed different patient groups and outcomes.

Given the heterogeneity of lung disease in COPD it is unlikely that one technique is superior for all patients. The choice of technique depends on the patient's condition (e.g. extent of airflow limitation, severity of dyspnoea); sputum volume; the effects of the different techniques on lung volumes, expiratory flow and dynamic airway compression; cognitive status of the patient and acceptability of the technique to the patient especially where long-term treatment is required.[113] Re-evaluation of the choice of airway clearance technique is necessary during an acute exacerbation of COPD when deterioration in lung function, increased sputum volume and increased work of breathing are likely to be present.

O6.6 Nutrition

In patients with COPD, both excess and low weight is associated with increased morbidity. Excessive weight increases the work of breathing and predisposes to sleep apnoea — both central hypoventilation and upper-airway obstruction. Progressive weight loss or body mass index < 20 are important prognostic factors for poor survival [114],[115],[116] [evidence level I]. This may be the result of a relative catabolic state (related to high energy demands of increased work of breathing) added to disturbance of nutritional intake (related to breathlessness while eating). Deleterious consequences include combined protein–energy malnutrition,[115] and possibly mineral or essential vitamin and antioxidant deficiencies.[115]

Randomised controlled trials of nutritional support in COPD have not shown significant improvements in nutrition, exercise capacity or other outcomes[116] [evidence level I]. Patients with COPD should not eat large meals, as this can increase dyspnoea. Several small nutritious (high energy, high protein) meals are better tolerated. Snacks may provide a useful addition to energy and nutrient intake. Referral to a dietitian for individual advice may be beneficial.

Anabolic steroids in patients with COPD with weight loss increase body weight and lean body mass but have little or no effect on exercise capacity.[117, 118]

O7. Co-morbidities & drug safety

O7.1 Aspiration

Aspiration of food and liquid is common in COPD and may be the cause of recurrent exacerbations and complications, such as pneumonia and patchy pulmonary fibrosis.

Diagnosis is usually easy with an adequate history from patients and their partners or carers. Dry biscuits and thin fluids cause the most difficulty. Confirmation rests with assessment by a speech therapist/ pathologist and videofluoroscopy.

Treatment involves retraining in safe swallowing techniques, which may include:

- avoiding talking when eating;
- sitting upright;
- taking small mouthfuls;
- chewing adequately;
- drinking with dry foods;
- using a straw; and
- drinking thickened fluids.

O7.2 Gastro-oesophageal reflux

In patients with COPD, hyperinflation, coughing and the increased negative intrathoracic pressures of inspiration may predispose to reflux, especially during recumbency and sleep. A cross-sectional questionnaire-based study found an increased rate of gastro-oesophageal reflux was associated with increased COPD exacerbations[119] but this finding has not been addressed prospectively. Microaspiration of oesophageal secretions (possibly including refluxed gastric content) is a risk, especially with coexistent snoring or OSA. Reflux and microaspiration exacerbate cough, bronchial inflammation and airway narrowing.

Diagnosis may be confirmed by 24-hour monitoring of oesophageal pH, modified barium swallow or gastroscopy. However, a therapeutic trial of therapy with H2-receptor antagonists or a proton-pump inhibitor may obviate the need for invasive investigations. Lifestyle changes, including stopping smoking, limiting food intake within 4 hours of bed-time, reduced intake of caffeine and alcohol, weight loss and exercise, will also help. Elevation of the head of the bed is also recommended.

Randomised controlled trials of these interventions are required.

O7.3 Alcohol and sedatives

Patients with COPD have impaired gas exchange and an exaggerated fall in Po2 with recumbency and sleep onset.[120],[121] Excessive use of alcohol and sedatives exacerbates this and predisposes to sleep-disordered breathing.

Heavy cigarette smoking is associated with misuse of other substances in many individuals. Nicotine, caffeine and alcohol also predispose to gastro-oesophageal reflux.

O7.4 Sleep related breathing disorders

COPD has adverse effects on sleep quality, resulting in poor sleep efficiency, delayed sleep onset, multiple wakenings with fragmentation of sleep architecture, and a high arousal index. Arousals are caused by hypoxia, hypercapnia, nocturnal cough and the pharmacological effects of methylxanthines and b-adrenergic agents.[122] Intranasal oxygen administration has been shown to improve sleep architecture and efficiency, as well as oxygen saturation during sleep.[120]

Indications for full diagnostic polysomnography in patients with COPD include persistent snoring, witnessed apnoeas, choking episodes and excessive daytime sleepiness. In subjects with daytime hypercapnia, monitoring of nocturnal transcutaneous carbon dioxide levels should be considered to assess nocturnal hypoventilation. Patients with COPD with a stable wakeful Pao2 of more than 55mmHg (7.3kPa) who have pulmonary hypertension, right heart failure or polycythaemia should also be studied. Overnight pulse oximetry is also useful in patients with COPD in whom long-term domiciliary oxygen therapy is indicated (stable Pao2 <55mmHg, or 7.3kPa) to determine an appropriate oxygen flow rate during sleep.

The overlap syndrome: The combination of COPD and obstructive sleep apnoea (OSA) is known as the “overlap syndrome”. The prevalence of COPD in unselected patients with OSA is about 10%, while about 20% of patients with COPD also have OSA.[121] Patients with COPD who also have OSA have a higher prevalence of pulmonary hypertension and right ventricular failure than those without OSA.[121] There is frequently a history of excessive alcohol intake. While oxygen administration may diminish the degree of oxygen desaturation, it may increase the frequency and severity of hypoventilation and lead to carbon dioxide retention.

As in other patients with OSA, weight reduction, alcohol avoidance and improvement of nasal patency are useful in those with COPD. Nasal continuous positive airway pressure (CPAP) is the best method for maintaining patency of the upper airway and may obviate the need for nocturnal oxygen. If nasal CPAP is not effective, then nocturnal bi-level positive airway pressure ventilation should be considered, although the benefits of this in chronic stable COPD remain to be established. The role of other OSA treatments, such as mandibular advancement splinting, remains to be evaluated in the overlap syndrome.

O7.5 Ostoporosis

Prevent or treat osteoporosis

Patients with COPD are at increased risk for fracture due to the disease itself, the use of high dose glucocorticoids and coexisting risk factors such as hypogonadism (induced by glucocorticoid therapy itself in high doses in men and women), immobilization reduced muscle mass and other factors. These patients may have reduced bone mineral density (BMD) due to a reduction in bone formation and perhaps increased bone resorption, the latter being primarily due to the underlying disease itself.

There is little evidence of a deleterious effect of inhaled glucocorticoid at conventional doses (<2, 200 mcg/day) on fracture risk. However, triamcinolone was associated with reduced BMD in the Lung Health Study[123] [evidence level II]. Australian Guidelines on the prevention and treatment of osteoporosis, including glucocorticoid-induced osteoporosis have been published.[124] Information on the current subsidies relevant to these drugs can be found on the website of the Pharmaceutical Benefits Scheme (www.pbs.gov.au/html/healthpro/search/results?atc-code=M05B&publication=GE) Higher doses of inhaled glucocorticoids are associated with suppressed biochemical markers of remodelling but data on BMD and fractures at these doses are not available[125] [evidence level I].

Despite the lack of evidence, management strategies in individuals taking long term glucocorticoid therapy should include investigation of fracture risk including bone densitometry, assessment of vitamin D status, and other risk factors such as coexisting illnesses that may influence the skeleton (e.g. primary hyperparathyroidism). In individuals with low BMD at onset and in those taking more than 10-15mg of prednisolone per day or who have several risk factors for osteoporosis and whose BMD is <1.5 standard deviations below the young adult mean, treatment should be considered.

Evidence for fracture risk reduction is available for alendronate, risedronate, etidronate and parathyroid hormone. There is no evidence that calcitriol reduces fracture risk and some evidence to the contrary, so that the use of this drug is not recommended[126] However, most patients in these studies did not have respiratory disease. Although calcium supplementation has not been demonstrated to reduce the risk of fracture in osteoporosis, a reduction in remodelling rate with some possible benefit in slowing bone loss is possible so calcium supplements are appropriate. Any deficiency of vitamin D should be corrected with supplements.

O8. Hypoxaemia and pulmonary hypertension

Identify and treat hypoxaemia and pulmonary hypertension [127-136] [evidence level I]

Pulmonary hypertension in patients with COPD results mainly from vasoconstriction of pulmonary arterioles in response to local hypoxia, usually resulting from impaired ventilation, and vasoconstrictor peptides produced by inflammatory cells.[127-130] The vasoconstriction minimises blood flow through poorly ventilated lung, reducing the mismatch of ventilation and perfusion. While this compensatory mechanism initially helps to maintain blood gas levels, the price is increased pulmonary vascular resistance, ultimately leading to right ventricular strain and failure (cor pulmonale). The vasoconstriction is reversible initially, but vascular remodelling occurs eventually and the condition becomes irreversible. In pulmonary emphysema there is also an anatomical disruption of capillaries in alveolar walls.

Right ventricular hypertrophy is seen in about 40% of patients with an FEV_1 less than 1.0L and in 70% of those with an FEV_1 less than 0.6L.[7] The presence of hypercapnia is strongly associated with cor pulmonale.[7]

When pulmonary hypertension and cor pulmonale seem out of proportion with the severity of airway narrowing, the additional factors that need to be considered include:

- sleep apnoea (central and obstructive);
- polycythaemia;
- recurrent pulmonary thromboembolism; and
- nocturnal hypoxaemia due to hypoventilation or supine gas exchange problems.

The development of pulmonary hypertension and peripheral oedema is a poor prognostic sign in COPD.[131] If untreated, the five-year survival rate is about 30%. Pulmonary hypertension is difficult to detect on clinical evaluation in patients with COPD.

Chest x-rays may show enlargement of proximal pulmonary arteries, but right ventricular enlargement is difficult to detect because of hyperinflation. Right axis deviation and P pulmonale on ECG may be difficult to detect because of low voltage traces (also a result of hyperinflation). Multifocal atrial tachycardia and atrial fibrillation are common.

Echocardiography is the best non-invasive method of assessing pulmonary hypertension but image quality is reduced by hyperinflation. This can be clarified using the more invasive procedure of trans-oespohageal echocardiography. Patients with COPD may have poor quality images on transthoracic examination and transoesophageal echocardiography may be frequently needed. Echocardiography is indicated in patients with severe disease, or when symptoms seem out of proportion to the severity of airflow limitation. Estimation of pressure relies on at least some tricuspid regurgitation. Other findings include mid-systolic closure of the pulmonic valve and increased right ventricular wall thickness.

O8.1 Treatment

Treat underlying lung disease: The logical first step is to optimise lung function and treat all potential aggravating conditions.

Oxygen therapy: Long term, continuous (>15h/day) oxygen therapy to treat chronic hypoxaemia prolongs survival of patients with COPD, presumably by reducing pulmonary hypertension.[21],[22, 131-133] (For a detailed description of oxygen therapy in COPD, see **Section P**).

Ventilatory support: For patients with COPD who also have sleep apnoea or hypoventilation, ventilatory support with continuous positive airway pressure (CPAP) or non- invasive positive pressure ventilation (NIPPV) may be more appropriate than oxygen therapy (for more details see **Section X**). The effectiveness of NIPPV for chronic respiratory failure due to COPD remains unproven. A systematic review comparing NIPPV to a range of other interventions including spontaneous breathing and sham ventilation, identified six RCTs and nine non-RCTs[137]. The RCTs found no significant improvement in outcomes for NIPPV. Arterial blood gases were no different; weighted mean difference for Pao2 was 1.86mmHg (95% CI -0.60 to 4.32) and for PaCo2 was -1.20mmHg (95% CI -5.05 to 2.65) for NIPPV compared to control. Few studies could be compared for analyses of symptoms, HRQoL, mortality or use of health resources but no significant difference was found between interventions.

The efficacy of NIPPV for long-term treatment has not yet been proven.[120],[134-136] Although preliminary studies have suggested that the addition of NIPPV to long-term therapy may have some beneficial effects on CO2 retention and shortness of breath, based on a 12-month study[138] and a 24-month study[139] in stable COPD patients with chronic respiratory failure, its widespread use cannot be advocated as yet.[140] However, compared with long-term oxygen therapy alone, the addition of NIPPV has some beneficial effects on CO2 retention and shortness of breath.[139]

Diuretics: Diuretics may reduce right ventricular filling pressure and oedema, but excessive volume depletion must be avoided. Volume status can be monitored by measuring serum creatinine and urea levels. Diuretics may cause metabolic alkalosis resulting in suppression of ventilatory drive.

Digoxin: Digoxin is not indicated in the treatment of cor pulmonale and may increase the risk of arrhythmia when hypoxaemia is present.[7] It may be used to control the rate of atrial fibrillation.

Vasodilators: Vasodilators (hydralazine, nitrates, nifedipine, verapamil, diltiazem, angiotensin-converting enzyme [ACE] inhibitors) do not produce sustained relief of pulmonary hypertension in patients with COPD.[141], [142] They can worsen oxygenation (by increasing blood flow through poorly ventilated lung) and result in systemic hypotension. However, a cautious trial may be used in patients with severe or persistent pulmonary hypertension not responsive to oxygen therapy. Some vasodilators (eg, dihydropyrodine calcium antagonists) have been shown to reduce right ventricular pressure with minimal side effects and increased well-being, at least in the short term [143], [144] Nitric oxide worsens V/Q mismatching and is therefore contraindicated in patients with COPD.[141],[142]

O9. Surgery

> In selected patients, a surgical approach may be considered for symptom relief [145-154],[155][evidence level III-2].

None of the current surgical approaches in patients with COPD provides a survival advantage.[7],[145] In view of the potential for serious morbidity and mortality, all surgical treatments require careful assessment by an experienced thoracic medical and surgical team.

O9.1 Bullectomy

This operation involves resection of large bullae (larger than 5cm). The procedure is most successful where there are very large cysts compressing adjacent apparently normal lung.[146-148]

O9.2 Lung volume reduction surgery

Lung volume reduction surgery (LVRS) involves resection of the most severely affected areas of emphysematous, non-bullous lung.[149] This can improve lung elastic recoil and diaphragmatic function.[150] LVRS is still an experimental, palliative, surgical procedure. The National Emphysema Treatment Trial was a large randomised multicentre study which investigated the effectiveness and cost-benefit of this procedure.[154] A total of 1,218 patients with severe emphysema underwent pulmonary rehabilitation and were then randomised to LVRS or continued medical therapy. Pulmonary rehabilitation plays an important role in preparing patients for interventions such as lung volume reduction.[156] There was no overall survival advantage of surgery, but after 24 months there was significant improvement in exercise capacity in the surgical group. Among patients with predominantly upper lobe emphysema and impaired exercise capacity, mortality was significantly lower in the surgical than the medical group. However, high risk patients with diffuse emphysema and well preserved exercise capacity are poor candidates for surgery because of increased mortality and negligible functional gain[157] [evidence level II].

O9.3 Lung Transplantation

Lung transplantation is indicated for selected patients with chronic end stage lung disease who are failing maximal medical therapy. However a survival benefit has not been demonstrated in emphysema. For most patients, transplantation is a palliative rather than a curative treatment. The International Society for Heart and Lung Transplantation has listed a number of contraindications.[158] The absolute contraindications include malignancy and untreatable advanced dysfunction of another major organ system. Relative contraindications include age older than 65 years, severely limited functional status and other medical conditions that have not resulted in end stage organ damage. The consensus guidelines[158] recommend transplantation be considered in COPD patients with:

- BODE index of 7 – 10 or at least one of the following:
- History of hospitalisation for exacerbations associated with acute hypercapnia
- Pulmonary hypertension or cor pulmonale or both, despite oxygen therapy
- FEV_1 < 20% and either DLco < 20% or homogeneous emphysema[157]

The experience of one Australian lung transplantation centre has recently been reviewed.[159] Over a 14 year period, 173 single lung, bilateral lung and heart lung transplants were performed for COPD. Perioperative survival (30 days) was 95% with deaths from infection, cerebrovascular accidents and multiorgan failure. The one, five and ten year survival rates were similar for patients with smoking related emphysema and α1 antitrypsin deficiency at 86%, 57% and 31% respectively. Survival in smoking related emphysema was better following bilateral than single lung transplantation. The commonest cause of late mortality was chronic rejection manifest as the bronchiolitis obliterans syndrome. Overall survival was comparable to international experience and similar to other forms of solid organ transplantation.

O10. Palliation and end of life issues

The World Health Organisation defines palliative care as an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

The goals of palliation are the elimination or attenuation of symptoms where the underlying cause remains irreversible or resistant to therapy. The risks and benefits of each treatment must be reviewed for individual patients so as to maximise comfort and function. One of the most concise and comprehensive resources for symptom control is the therapeutic guidelines for palliative care www.tg.com.au/index.php?sectionid=47

Despite appropriate treatment, the trajectory of COPD is one of increasing disability and morbidity with time. As the severity of the disease increases quality of life is reduced, more frequent complications require treatment and increasing dependency impacts on carers. Unlike the cancer trajectory, the intermittent and potentially reversible acute exacerbations of COPD make palliative referral and discussion about end of life care difficult to initiate[160]. Palliative care services have evolved into integrated systems of multidisciplinary care focussing on symptom control and support in hospital, community or hospice.

Compared to cancer patients:

- COPD patients were more likely to have poor symptom control[161]
- COPD patients were more likely to die in hospital[162]
- COPD patients were less likely to receive palliative support[162]

The Gold standards framework suggests three triggers for supportive or palliative care[163]:

- Would you be surprised if this patient were to die in the next 6-12 months?
- Has the patient made a choice for comfort care only, treatment limitations (maintenance therapy) or do they have a special need for supportive or palliative care?
- Specific clinical indicators of severe COPD

O10.1 Opioids

Opioids may have a role for patients with severe intractable dyspnoea[164] [evidence level I]. Opioids have a small but statistically significant benefit in reducing dyspnoea [evidence level I]. In one study, the most significant side effect was constipation and there was no significant increase in respiratory depression, sedation or nausea and vomiting[165]. Nonetheless, opioids should be used with care in COPD. There is little evidence to support nebulised opioids in the treatment of breathlessness[164]. The opioid dose required for symptom control should be established by titration, starting at a low dose and increasing until efficacy is achieved. There is little comprehensive evidence to guide clinicians on the use of opioids in COPD symptom control.

O10.2 Advanced Care Plans

General practitioners could begin the discussion with patients about the course of their disease. Consideration should be given to appointing an Enduring Power of Attorney (EPOA) for financial matters, as well as an EPOA for medical management. There are multiple online resources, e.g. Office of the Public Advocate: www.legalaid.vic.gov.au/cl.medical_fact.pdf, but these are also available through any solicitor or legal service and may vary between States of Australia. Over time, physicians may need to introduce topics of choices regarding intubation, admission (or not) to ICU and patients' views on "not for resuscitation" or medical treatment orders. This may involve a discussion regarding quality of life and choices they may wish to consider.

Issue for discussion could include Advanced Health Care Directives. It is crucially important that next of kin, medical carers and their family solicitors are aware of the existence of these legal documents. They are of course useless residing in a drawer at the patient's home unknown to those who can enact their directives. The discussion about pros and cons of intubation and easy vs. difficult weaning from intubation (including the concept of tracheostomy) may need input from a respiratory physician, but it is ultimately up to the patient's general practitioner to begin the discussion and not leave it too late in the patient's disease course.

O10.3 Palliative oxygen therapy for dyspnoea

There is little evidence to support the use of oxygen therapy in patients with dyspnoea and mild hypoxaemia.[166] The prescription of oxygen in these clinical situations should be made on an individual basis.[167] Oxygen therapy should perhaps be considered following a trial of opioid or anxiolytic agent to control dyspnoea.

P: Prevent deterioration

Reducing risk factors for COPD is a priority, and smoking is the most important of these. Reduction of exposure to occupational dust, fumes and gases and to indoor and outdoor air pollutants is also recommended.[7] Influenza vaccination reduces the risk of exacerbations and death [evidence level I], while long term oxygen therapy reduces mortality [evidence level I].

P1. Risk factor reduction

P1.1 Smoking cessation

> Smoking cessation reduces the rate of decline of lung function[8],[19],[20] [evidence level I]

A comprehensive review of smoking cessation in patients with respiratory diseases has been published by the European Respiratory Society (www.ersnet.org/ers/lr/browse/viewPDF.aspx?id_attach=17030)[168] A successful tobacco control strategy involves integration of public policy, information dissemination programs and health education through the media and schools.[7] Smoking prevention and cessation programs should be implemented and be made readily available[7],[169] [evidence level I]. Pharmacotherapies double the success of quit attempts. Behavioural techniques further increase the quit rate. [170],[171],[172],[173],[174],[175],[176] [evidence level I]

People who continue to smoke despite having pulmonary disease are highly nicotine dependent and may require treatment with pharmacological agents to help them quit.[170] [171]

Smoking cessation interventions have been shown to be effective in both sexes, in all racial and ethnic groups tested, and in pregnant women.[7] International data show that smoking cessation strategies are cost effective, but with a 10-fold range in cost per life-year gained depending on the intensity of the program and the use of pharmacological therapies.[7] A range of health professionals can help smokers quit[177],[178],[179], but relapse is common. [evidence level I]

Brief counselling is effective [evidence level I] and every smoker should be offered at least this intervention at every visit.[7] Personalising smoking cessation advice based on lung function results increase cessation rates.[180] Currently accepted best practice is summarised in the 5-A strategy:[7]

- **A**sk and identify smokers
- **A**dvise smokers about the risks of smoking and benefits of quitting and discuss options
- **A**ssess the degree of nicotine dependence and motivation or readiness to quit
- **A**ssist cessation — this may include specific advice about pharmacological interventions or referral to a formal cessation program if available
- **A**rrange follow-up to reinforce messages

Cessation of smoking is a process rather than a single event, and smokers move between various stages of being not ready (pre-contemplation), unsure (contemplation), ready (preparation), quitting (action) and possibly relapsing (maintenance) before achieving long-term success. The most strenuous efforts should be made with those smokers ready to quit or quitting. Cessation rates increase with the amount of support and intervention, including practical counselling and social support arranged outside of treatment.

P1.2 Treatment of nicotine dependence

> Treatment of nicotine dependence is effective and should be offered to smokers in addition to counselling[181][evidence level I]

Pharmacotherapies for nicotine dependence are effective and should be added to counselling if necessary and in the absence of contraindications [7] [evidence level I].

Caution is recommended in people with medical contraindications, light smokers (< 10 cigarettes a day) who may become dependent on nicotine replacement therapy, pregnant women and adolescent smokers.[7] There is no evidence as to which pharmacotherapy should be offered as initial treatment.

P1.2.1 Nicotine replacement therapy

All forms of nicotine replacement therapy (NRT) appear to be useful in aiding smoking cessation. [182] NRT is most suitable for highly dependent smokers who are motivated to quit. There is little evidence for its role in those who smoke up to 15 cigarettes daily. The choice of type of NRT depends on patient preference, needs and tolerance. NRT is more effective when combined with counselling and behavioural therapy.[183]

NRT is safe in patients with stable cardiac disease such as angina pectoris [evidence level I].[7],[171] NRT produces lower peak levels of nicotine than active smoking, so theoretically, should be safer than smoking, even in patients with unstable disease.

Nicotine transdermal patch: A steady nicotine level (about half that of smoking) is maintained to reduce withdrawal symptoms. However, the patch does not provide the peak nicotine levels of smoking which reinforce the addiction. Patch use increases the sustained quit rate at 12 months compared with placebo (OR=1.51, 95% CI 1.35 to 1.70, 10,928 participants, NNT=25, 95% CI 19 to 36). The strength of patch recommended depends on the degree of nicotine dependence, indicated by number and strength of cigarettes smoked daily. A range of strengths are available in both 24 hour and 16 hour patches durations, although there is no evidence of increased efficacy for longer duration of action. Using higher doses produces higher blood nicotine levels and provides more relief of morning cravings, but only produces a small increase in efficacy (OR=1.15, 95% CI 1.01 to 1.30, 4,634 participants) Six to eight weeks of use are generally recommended, with no evidence of increased efficacy for longer durations, and tapering of the nicotine dose over this time, often occurs, although there is no evidence of increased efficacy (OR=0.99, 95% CI 0.74 to 1.32, 264 participants). The only significant side effect is skin irritation, which is generally mild and rarely leads to cessation of use.

Nicotine gum: Nicotine is rapidly absorbed through the oral mucous membrane, so gum should be chewed only two to three times per minute to avoid excessive salivation, swallowing of nicotine and gastrointestinal side effects. The blood levels achieved by nicotine chewing gum are one-third (2 mg gum) or two-thirds (4 mg gum) those of smoking. Nicotine gum also increases the sustained 12 month quit rate compared to placebo (OR=1.43 95% CI 1.31 to 1.56). The 4mg dose gum is more effective than the 2mg in high dependency smokers (OR=1.85 95% CI 1.36 to 2.50, 618 participants), but there is no significant difference between them in efficacy for low dependency smokers. Patients should taper the dose gradually, but dependence on the gum can occur in up to 20% of users. Most patients should have stopped using the gum within three months.

Nicotine lozenge: Nicotine lozenges are available in 2 mg and 4 mg doses and increase quit rates over placebo measured at 6 months or beyond (OR=2.00 95% CI 1.63 to 2.45, 3,109 participants). No special technique is required — the lozenge is held in the mouth and moved around periodically until it dissolves. As the lozenge dissolves, it releases about 25% more nicotine than the equivalent dose of gum. Patients should reduce the number of lozenges they are using over 12 weeks, remaining on the same strength lozenge throughout. Lozenges may be preferable for denture wearers who wish to use oral NRT.

Nicotine inhaler: The nicotine inhaler consists of a plastic mouthpiece and cartridge containing 10 mg of nicotine. The inhaler produces nicotine concentrations that are a third those achieved with smoking. The inhaler is useful for smokers who miss the hand-to-mouth action of smoking, or who have problems with the gum. The inhaler increases the quit rate over placebo measured at 6 months or beyond (OR=1.90 95% CI 1.36 to 2.67, 976 participants). The recommended maximum period of use is 16 weeks.

P1.2.2 Antidepressants

Antidepressants for smoking cessation have been shown to be effective in a number of trials which have been pooled in a Cochrane systematic review. [184] This review included a total of 53 trials, 40 of which assessed the effect of bupropion and eight nortriptyline. Pooling six available trials using nortriptyline as the only pharmacotherapy showed evidence of a significant benefit for nortriptyline over placebo in achieving cessation in the longer (6-12 months) term (N = 975, OR 2.34, 95% CI 1.61 to 3.41, NNT = 10, 95% CI 6 to 20)). Nortriptyline has the potential for serious adverse effects, but it was not possible to pool adverse effects from the few small trials for smoking cessation. While none of the included trial reported major adverse effects, individual studies did report an increased incidence of anticholinergic adverse effects such as dry mouth and constipation.

Bupropion, when used as the sole pharmacotherapy, doubled the odds of smoking cessation compared to placebo at ≥6 months (31 trials, OR 1.94, 95% CI 1.72 to 2.19, NNT = 13, 95% CI 11 to 17). There were few serious adverse effects reported, although it is known there is a risk of about 1 in 1000 of seizures associated with bupropion use, and as a result it is contraindicated in patients with epilepsy, bulimia or a history of head trauma. While minor adverse effects could not be pooled, individual trials frequently reported insomnia, dizziness and headache to be more common with bupropion than placebo. Initial concerns that bupropion may increase suicide risk are currently unproven. Bupropion is recommended as first-line pharmacotherapy for smoking cessation alongside NRT [evidence level I],[7] but there are currently insufficient data to recommend its use in preference to NRT, or vice versa. The recommended dose is 150 mg orally once daily for three days, then 150 mg twice daily (at least eight hours apart) for between seven and nine weeks, in combination with counselling. A quit date should be set (e.g. Day 5–10). The drug works equally well in smokers with and without a past history of depression. It is also effective in people who have relapsed and are motivated to quit again. There is insufficient evidence that adding bupropion or nortriptyline to nicotine replacement therapy provides an additional long-term benefit. Three trials of extended therapy with bupropion to prevent relapse after initial cessation did not find evidence of a significant long-term benefit.

The Cochrane systematic review included six trials of selective serotonin reuptake inhibitors; four of fluoxetine, one of sertraline and one of paroxetine. None of these detected significant long-term effects, and there was no evidence of a significant benefit when results were pooled. There was one trial of the monoamine oxidase inhibitor moclobemide, and one of the atypical antidepressant venlafaxine, neither of which detected a significant long-term benefit. Bupropion may interact with other antidepressants, especially monoamine oxidase inhibitors, which require a 14-day washout.

P1.2.3 Nicotine Receptor Partial Agonists

The addictive properties of nicotine are considered to be mediated through its action as an agonist at alpha4beta2 nAnti-Cholinergic Receptors (α4β2 nAChR), which stimulate the release of dopamine. [185] Varenicline was developed to counteract the effects of nicotine on the nAChRs, and its efficacy in smoking cessation has been assessed in a Cochrane systematic review. [186] In five trials of varenicline compared to placebo for smoking cessation, it was found to be significantly more effective for continuous abstinence at 12 months than placebo (n = 2023, OR 3.22, 95% CI 2.43 to 4.27, NNT = 8, 95% CI 6 to 11). A 12-week course of treatment is recommended, starting 1–2 weeks before the quit date and titrating the dose as follows: days 1–3: 0.5 mg daily; days 4–7: increase to 0.5 mg twice daily; and continue with 1 mg twice daily from day 8 to the end of a 12-week treatment course. Although adverse effects could not be pooled for analysis in the systematic review, multiple trials reported an increased incidence of minor effects, particularly nausea, which was mostly at mild to moderate levels and usually subsided over time, but also insomnia and abnormal dreams. People planning to use the drug should set a date to stop smoking and be warned that varenicline frequently causes nausea which may settle over time and taking it with food and a full glass of water may help reduce nausea. As varenicline is a new drug in a new class of drugs, uncertainty exists about its safety profile and there have been some post-marketing reports of new onset of depressed mood, aggressive and erratic behaviour, suicidal thoughts and suicide within days to weeks of starting in patients with and without pre-existing psychiatric illness.(U S Food and Drug Administration. FDA Medwatch: Chantix (Varenicline). 2007. http://www.fda.gov/medwatch/safety/2007/safety07.htm#Chantix; Medicines and Healthcare products Regulatory Agency (MHRA). Varenicline: possible effects on driving; psychiatric illness. Drug safety update 2007; 1: 12) Varenicline has no known clinically meaningful interactions with other drugs. Two trials have tested the use of varenicline beyond the 12-week standard regimen and found the drug to be well-tolerated and effective during long-term use. Three studies comparing varenicline with bupropion found it to be significantly more effective in achieving continuous abstinence at one year (n = 1,622, OR 1.66, 95% CI 1.28 to 2.16, NNT = 14, 95% CI 9 to 32). A recent open-label study comparing varenicline with NRT did not find any difference in one-year cessation rates, despite higher abstinence at the end of treatment. [187]

P1.2.4 Cannaboid Type 1 Receptor Antagonists

Central cannabinoid (CB1) receptors have recently been implicated in brain reward function, and are thought to have a role in controlling food consumption and in dependence and habituation. Repeated nicotine use may also over stimulate the endocannabinoid system and receptor antagonists may work by selectively blocking the CB1 receptors, thereby restoring the balance and inhibiting nicotine and food cravings. Rimonabant is the first selective cannabinoid type 1 receptor antagonist to have been produced and clinically tested, although is yet to be marketed in Australia. It was developed initially as a possible treatment for obesity, but it has also been proposed as an aid to smoking cessation and has potential to protect successful quitters from post-cessation weight gain, thereby addressing smokers' reluctance to persist with a quit attempt because of concerns over weight gain. [188] A Cochrane systematic review has assessed the effect of rimonabant compared to placebo in aiding smoking cessation. [189] In 2 trials suitable for inclusion in the review, rimonabant 20mg significantly increased the one-year cessation rate compared to placebo (n = 1049, OR 1.61, 95% CI 1.12 to 2.30, NNT = 18, 95% CI 10 to 87). Adverse events included nausea and upper respiratory tract infections, and weight gain was reported to be significantly lower among the rimonabant 20 mg quitters than in the placebo quitters. During treatment, overweight or obese smokers tended to lose weight, while normal weight smokers did not.

P1.2.5 Other agents

A number of other agents have been shown to be effective in smoking cessation, but are not commonly used in clinical practice. Clonidine, an antihypertensive agent, increased smoking cessation 12 weeks following the end of treatment compared to placebo, although abstinence was not objectively confirmed in all studies (risk ratio 1.63, 95% CI 1.22 to 2.18, NNT = 12, 95% CI 6 to 32). There was a high incidence of dose-dependent adverse effects, particularly dry mouth and sedation. [190] Anxiolytics have not been shown to be effective in smoking cessation. A Cochrane systematic review including one trial each of diazepam, meprobamate, metoprolol and oxprenolol and two trials of buspirone concluded there was no strong evidence of an effect for any of these drugs, but confidence intervals were wide, and an effect of anxiolytics cannot be ruled out on current evidence. [191]

P1.3 Prevent smoking relapse

Family, friends and workmates should be advised of the intention to quit and asked to provide understanding and support. The relapse rate is increased if there are other smokers in the household. Success is more likely if all the smokers agree to quit together. Suggest the patient ring the Quit Line or other local services (Australia, **131 848**; NZ, **0800 778 778**).

Ex-smokers who attend for follow-up are more likely to be successful in the long term. Support is most needed in the first few weeks, so regular follow-up visits then and over the first three months should be encouraged.

P2. Influenza vaccination

> Influenza vaccination reduces the risk of exacerbations, hospitalisation and death[192],[193] [evidence level I]

Annual influenza vaccination reduces by about 50% the development of severe respiratory complications and hospitalisation or death from both respiratory disease and all causes[192],[193] [evidence level I]. The vaccine used in Australia does not contain a live virus and cannot cause an infection. Side effects include a sore arm the following day and possibly a mild fever and arthralgia at five to eight days caused by the immune response. The vaccine usually contains three strains (2A and 1B), which are adjusted annually based on epidemiological data. It should be given in early autumn to all patients with moderate to severe COPD.[192] ,[193] A second vaccination in winter increases antibody levels.[7]

P3. Pneumococcal vaccination

Pneumococcal vaccination is known to be highly effective in preventing invasive bacteraemic pneumococcal pneumonia, but may be less effective in elderly or immunosuppressed patients.[194] There is no direct evidence of its efficacy in preventing pneumococcal exacerbations of COPD,[195] but prevention of pneumonia in these patients with already reduced respiratory reserve is a worthy goal in its own right,[194, 196, 197] so pneumococcal vaccination (polyvalent covering 23 virulent serotypes) is recommended in this group [evidence level II].[7] There is no evidence or rationale for vaccinating more frequently in COPD. NHMRC guidelines recommend pneumococcal vaccination for:

- Over 65s – free vaccination from 1st January 2005, aged 50 for indigenous patients;
- Chronic cardiovascular or pulmonary disease and those who smoke;
- Pneumovax 1 dose 0.5mL re-vaccination at 5 and 10 years for both indigenous and non-indigenous patients

Please see the website below for further details:
http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/content/handbook-pneumococcal

P4. Haemophilus influenzae vaccination

Six randomised trials of oral monobacterial whole cell killed non-typable haemophilus influenzae vaccine[198] found a significant reduction in the incidence of bronchitic episodes three months after vaccination, but the effect had disappeared by nine months. The severity of exacerbations in the treatment group as measured by the requirement to prescribe antibiotics was reduced by 65% at six months. However, a larger clinical trial is needed to assess longer term prognosis. [evidence level I]. Furthermore, this is not currently available in Australia or New Zealand.

P5. Immuno-modulatory agents

The available evidence suggests that the putative immuno-modulatory agent OM-85 BV is well tolerated[199] [evidence level I]. However, consistent results across important clinical outcomes, such as exacerbation and hospitalization rates, are lacking to determine whether it is effective. Further randomized, controlled trials enrolling large numbers of persons with well-defined COPD are necessary to confirm the effectiveness of this agent.

P6. Antibiotics

Current evidence does not support long-term antibiotic use to prevent exacerbations in patients with COPD[200],[201] [evidence level I]. However, they should be used in exacerbations with an increase in cough, dyspnoea, sputum volume or purulence (see **Section X**).

Prophylactic antibiotics in chronic bronchitis/ COPD have a small but statistically significant effect in reducing the days of illness due to exacerbations of chronic bronchitis. However, they do not have a place in routine treatment because of concerns about the development of antibiotic resistance and the possibility of adverse effects. The available data are over 30 years old, so the pattern of antibiotic sensitivity may have changed and there is a wider range of antibiotics in use.[202]

P7. Anticholinergics

A Cochrane review of nine RCTs (6,584 patients) found that tiotropium reduced the odds of a COPD exacerbation (OR 0.74, 95% CI 0.66 to 0.83) and related hospitalisations (OR 0.64, 95% CI 0.51 to 0.82) compared to placebo or ipratropium. The number of patients who would need to be treated with tiotropium for one year was 14 (95% CI 11 to 22) to prevent one exacerbation and 30 (95% CI 22 to 61) to prevent one hospitalisation[54] [evidence level I]. Another systematic review of 22 trials with 15,276 participants found that anticholinergic use also significantly reduced respiratory deaths (RR 0.27, 95% CI 0.09 to 0.81) compared with placebo. It would be necessary to treat 278 patients with anticholinergic agents to prevent one death[203] [evidence level I].

P8. Glucocorticoids

The effect of inhaled glucocorticoids on the decline in lung function seen in COPD has been the subject of a series of controlled trials and systematic reviews over recent years, and the effect remains unclear. A Cochrane systematic review[80] that pooled results from 9 studies found no significant effect of inhaled glucocorticoids on the decline in lung function for studies of 2 years or longer duration, weighted mean difference = 5.8 mls/yr (95% CI) -0.28 to 11.88, 2,333 participants). However this analysis did not include a recently published large randomised controlled trial, the TORCH study[81], which did find a difference between inhaled fluticasone and placebo for the decline in lung function over 3 years, mean difference = 47 (95% CI 31 to 64, 2,617 participants, p<0.001) mls.

The Cochrane systematic review also found a significant effect of inhaled glucocorticoids on the decline in quality of life. For studies over 6 months duration this effect was a decrease in the mean fall in the St Georges Respiratory Questionnaire score of -1.22 (95% CI -1.83 to -0.60, 2,507 participants) units compared to placebo, although the studies were of varying duration from 12 to 36 months. This review did not include participants from the TORCH study, which also found a significant reduction in the decline in QOL for participants on fluticasone compared to placebo, mean difference -2.0 (95% CI -2.9 to -1.0, 2,479 participants, p<0.001).

While these data do not support the use of inhaled glucocorticoids in all people with COPD, they are indicated for those with more severe disease (FEV_1 <50% predicted), frequent exacerbations or a documented response to inhaled glucocorticoids. While the long-term adverse effects of inhaled glucocorticoids are unknown, caution is needed if ceasing inhaled glucocorticoid treatment given the observation that abrupt withdrawal maybe associated with increased symptoms.[83]

P9. Mucolytic agents

Mucolytics may reduce the frequency and duration of exacerbations[204] [evidence level II]

Mucolytics, including N-acetylcysteine (NAC), ambroxol (3), sobrerol, carbocysteine, sobrerol, letosteine, cithiolone, iodinated glycerol, N-isobutyrylcysteine (NIC), myrtol and erdosteine have multiple possible actions in COPD including decreasing sputum viscosity, and antioxidant, anti-inflammatory or antibacterial activity. A Cochrane review[204] was last updated in 2007 and included 5 studies in COPD and 21 studies in chronic bronchitis. The authors found treatment with mucolytics was associated with a small reduction in acute exacerbations, WMD -0.05 per month (95% CI -0.05 to -0.04) and a reduction in total number of days of disability WMD -0.56 (95% CI -0.77 to -0.35). This equated to a NNT of 6 to prevent one exacerbation over winter months, and they concluded mucolytics should be considered for use through the winter months at least, in patients with moderate or severe COPD in whom inhaled glucocorticoids are not prescribed. The caveat on the use of inhaled glucocorticoids was their belief that this was the cause of the decline in the observed effect of mucolytics over time. This is in keeping with a recent trial of 709 subjects with COPD randomized to carbocisteine or placebo (Zheng 2008), which found a significant decrease in exacerbations (risk ratio 0.75, 95% CI 0.62 to 0.92, p=0.004) in subjects where the use of inhaled glucocorticoids was only 15% in the placebo and 18% in the carbocisteine arms[205] [evidence level II].

P10. Regular review

Regular review, with objective measures of function and medication review, is recommended in the hope that this may reduce complications and the frequency or the severity (or both) of exacerbations and admissions to hospital.[7] Please see comments in S**ection D**.

P11. Oxygen therapy

Long-term oxygen therapy (more than 15 h/day) prolongs life in hypoxaemic patients (PaO_2 < 55 mmHg, or 7.3 kPa) [21],[22],, [131-133],[206],[207, 208] [evidence level I]

Long term oxygen therapy reduces mortality in COPD.[21],[22],[132,133],[206],[207, 208] It may also have a beneficial impact on haemodynamics, haematological status, exercise capacity, lung mechanics and mental state.[131],[133],[208] Although effective, it is a potentially expensive therapy that should only be prescribed for those in whom there is evidence of benefit (see below). Information on prescribing oxygen therapy is given in Appendix 3.

Long-term continuous oxygen therapy (at least 15 hours a day) is appropriate for patients who have Pao2 consistently < 55 mmHg (7.3 kPa; Spo2 88%)[21],[22]when breathing air, at rest and awake [evidence level I]. If oxygen is prescribed when the patient's condition is unstable (eg, during an exacerbation), then the requirement for it should be reviewed four to eight weeks after initiation. At assessment for ongoing therapy, the patient's condition must be stable, all potentially reversible factors must have been treated and the patient must have stopped smoking at least one month previously.

Polycythaemia (haemoglobin level > 170 g/L), clinical or electrocardiographic evidence of pulmonary hypertension, as well as episodes of right heart failure, are consistent with the systemic effects of chronic hypoxaemia, and continuous oxygen should be supplied if the stable Pao2 is 55– 59 mmHg (7.3–7.9 kPa; Spo2 < 90%).[207],[206] Continuous oxygen therapy is of most benefit for patients with increased arterial Paco2 (> 45 mmHg, or 6 kPa).[22]

Government funding is available on the basis that the prescribing doctor is an approved prescriber (usually a respiratory physician). Oxygen is usually supplied to patients meeting specific criteria and means testing by state or regional health departments in Australia and New Zealand.

Intermittent oxygen therapy: Available evidence does not allow any firm conclusions to be made about the effectiveness of long-term intermittent ambulatory domiciliary oxygen therapy in patients with COPD.[209] However, use of intermittent oxygen therapy may be considered for:

- People who experience oxygen desaturation on exertion.[209] A Cochrane review of 31 studies found that ambulatory oxygen was efficacious in single assessment studies when comparing an exercise test performed breathing oxygen or air in patients with moderate to severe COPD. Benefits were shown in endurance exercise capacity, dyspnoea at isotime and oxygen saturation.[210] However, the minimum clinically important difference in these variables with oxygen therapy is unknown, Because of the heterogeneity of the studies, subgroup analyses were not possible to determine which patients were more likely to benefit. Benefit cannot be predicted by a resting test. Acute benefit may be established by comparing exercise endurance on a walking test (e.g. six minute walk test, incremental or endurance shuttle walk test or treadmill test) when breathing oxygen and when breathing room air. The oxygen system used in the assessment should be the same as the system the patient would use if oxygen were prescribed (e.g. trolley or shoulder bag to transport the cylinder). A stationary bicycle should not generally be used for the test as oxygen desaturation is significantly greater in COPD patients when walking as compared to cycling. [211],[212],[213] Although oxygen may be used during exercise training with a similar aim, a systematic review of the small number of suitable studies reported to date does not allow a conclusion to be drawn about the use of oxygen in this circumstance.[214] As the relationship between single assessments and long-term benefits is unclear, the acute assessment should form only part of the determination and benefit of ongoing ambulatory oxygen therapy. Long-term review and determination of oxygen usage are also important[215];
- Patients living in isolated areas or prone to sudden life- threatening episodes while they are awaiting medical attention or evacuation by ambulance;
- Patients travelling by air. Flying is generally safe for patients with chronic respiratory failure who are on long- term oxygen therapy, but the flow rate should be increased by 1–2 L/minute during the flight (see also below).

It is to be noted that short-burst oxygen i.e. oxygen inhaled immediately prior and/or following exertion with the aim of relieving breathlessness or improving exercise tolerance is not effective[216] [evidence level I].

Nocturnal oxygen therapy: Patients with hypoxaemia during sleep may require nocturnal oxygen therapy. Nocturnal hypoxaemia should be considered in patients whose arterial gas tensions are satisfactory when awake, but who have daytime somnolence, polycythaemia or right heart failure. Oxygen is indicated for patients whose nocturnal arterial oxygen saturation repeatedly falls below 88%. Sleep apnoea should be excluded.

P11.1 Fitness to fly

Commercial aircraft operate at altitudes of up to 12 500 metres, with the plane's interior pressurised to 2100–2400 metres. At this "altitude" the alveolar Pao2 for healthy individuals decreases from 103 mmHg (13.7 kPa) to 64 mmHg (8.5 kPa) and oxygen saturation declines from 97% to 93%.

As a general rule, supplemental oxygen is unlikely to be required if the resting oxygen saturation is 95% or higher, and likely to be required if oxygen saturation is 88% or lower. Patients with oxygen saturation values between these levels might require specialist assessment.

Before flying, patients should ideally be clinically stable. Patients recovering from an acute exacerbation are particularly at risk. Those already on long-term oxygen therapy need an increase in flow rate of 1–2 L per minute during flight. Careful consideration should be given to any comorbidity that may impair delivery of oxygen to the tissues (eg, cardiac impairment, anaemia). Exertion during flight will exacerbate hypoxaemia.

The American Thoracic Society currently recommends that Pao2 during air travel should be maintained at more than 50 mmHg (6.7 kPa). At altitude, Pao2 can be estimated from Pao2 at sea level by means of published nomograms. If the Pao2 at sea level is less than 70 mmHg (9.3 kPa), Pao2 at 2300 metres is less than 50 mmHg (6.7 kPa). The natural conclusion is that all patients with a Pao2 less than 70 mmHg (9.3 kPa) at rest at ground level should receive supplemental oxygen.[206],[217]

Many lung function laboratories perform assessments for fitness to fly. These may include measurement of arterial blood gas levels or transcutaneous oxygen saturation while breathing a mixture of 15% oxygen and 85% nitrogen, which mimics conditions at 2800 metres.

D: Develop support network and self-management

COPD imposes handicap which affects both patients and carers[218, 219],[103, 220] [evidence level II]

In the early stages of disease, patients with COPD will often ignore mild symptoms, and this contributes to delay in diagnosis. As the disease progresses, impairment and disability increase. As a health state, severe COPD has the third-highest perceived "severity" rating, on a par with paraplegia and first-stage AIDS.[221] Depression, anxiety, panic disorder, and social isolation add to the burden of disease as complications and comorbidities accumulate. Patients with COPD often have neuropsychological deficits suggestive of cerebral dysfunction. The deficits are with verbal and visual short-term memory, simple motor skills, visuomotor speed and abstract thought processing.

People with chronic conditions are usually cared for by partners or family members. Significant psychological and physical consequences occur in carers of patients with chronic diseases. In populations where the patient's chronic disease is non-respiratory, there is evidence[222] that the psychological health status of carers and patients is linked. One of the most effective means of improving the patient's functional and psychological state is pulmonary rehabilitation.

Health systems around the world are reorienting health care delivery in ways that continue to provide services for people with acute and episodic care needs while at the same time meeting the proactive and anticipatory care needs of people with chronic diseases and multiple morbidities. Wagner and colleagues have articulated domains for system reform in their Chronic Care Model[5]. These include Delivery System Design (e.g. multi-professional teams, clear division of labour, acute vs. planned care); Self Management Support (e.g. systematic support for patients / families to acquire skills and confidence to manage their condition); Decision Support (e.g. evidence-based guidelines, continuing professional development programs) and Clinical Information Systems (e.g. recall reminder systems and registries for planning care)[223]. Although these domains are not specifically addressed in the following sections, they are directly relevant to each.

Disease management approaches in COPD include a number of the Chronic Care Model domains. A systematic review by Peytremann-Bridevaux[224] concluded that COPD disease management programs improve exercise capacity and health related quality of life, and reduce hospitalisation. These programs were defined as including interventions with two or more different components (e.g. physical exercise, self-management, structured follow-up) with at least one of these components continuing for 12 months, delivered by two or more health care professionals and incorporating patient education. In this review, it is unclear which specific components of the disease management programs contribute the most benefit to patients.

D1. Support team

Enhancing quality of life and reducing handicap requires a support team[206]

Patients and their family/friends should be actively involved in a therapeutic partnership with a range of health professionals[218],[220],[101, 104][evidence level II]

In advanced disease, the many comorbidities, social isolation and disability mean that a multidisciplinary approach to coordinated care may be appropriate. The general practitioner plays a key role in the delivery and coordination of care for people with chronic disease including COPD and can access a range of Medicare items to support the delivery of multi-disciplinary care. The multidisciplinary team, depending on local resources, may include the members listed below. The role of respiratory specialists is outlined in **Section C**.

D1.1 General Practitioner

As the primary healthcare provider, the GP is uniquely placed to identify smokers and help them quit, diagnose COPD in its early stages and coordinate care as the disease progresses.

Smoking cessation: A doctor's advice is an important motivator for smoking cessation, especially if the doctor is the family physician. The GP can help initiate the cycle of change by repeated brief interventions. Since relapse to smoking is common, GPs should make enquiries about smoking status routinely at each visit. There are several smoking cessation programs that have been developed for use in general practice. The GP is also the appropriate health professional to recommend or prescribe nicotine replacement therapy and pharmacological treatment of nicotine addiction (for a detailed discussion of smoking cessation interventions, see **Section P**).

Early diagnosis: Most people visit a GP about once a year. Simple questions relating to smoking history, daily cough and degree of breathlessness should lead to lung function testing.

Coordinate investigation and management: GPs will manage patients with mild to moderate COPD. Referral to a respiratory physician may be indicated to confirm the diagnosis, exclude complications and aggravating factors, and to help develop a self-management plan (**Section C, Box 8**).

Coordinate care in advanced disease: GPs play a crucial role coordinating services provided by a range of healthcare professionals and care agencies (the "multidisciplinary team").

D1.2 GP practice nurse/ nurse practitioner/ respiratory educator/ respiratory nurse

Specific aspects of care provided by these health professionals in COPD may include:

- respiratory assessment, including spirometry and pulse oximetry;
- implementation of, or referral for, interventions such as smoking cessation, sputum clearance strategies, oxygen therapy;
- skills training with inhalation devices;
- education to promote better self-management (eg, medications and response to worsening of symptoms);
- organisation of multidisciplinary case conferences and participation in care-plan development; and
- assessment of the home environment.

D1.3 Physiotherapist

Physiotherapists are involved in a broad range of areas, including exercise testing and training, assessment for oxygen therapy, patient education, sputum clearance, breathing retraining, mobility, non-invasive positive pressure ventilation, postoperative respiratory care (eg, after LVRS), and assessment and treatment of musculoskeletal disorders commonly associated with COPD.

D1.4 Occupational therapist

Occupational therapists provide specific skills in task optimisation and prescription for those with severe disease of adaptive equipment and home modifications. Some therapists also teach energy conservation for activities of daily living and can help in the set-up of home and portable oxygen.

D1.5 Social worker

Social workers can provide counselling for patients and their carers, organisation of support services, respite and long- term care.

D1.6 Clinical psychologist/psychiatrist

Anxiety and depression are common comorbidities in patients with COPD[225]. Panic disorder is also frequent, and can be disabling and out of proportion to the impairment of lung function. Clinical psychologists and psychiatrists can use techniques such as counselling and cognitive behavioural therapy to help address anxiety and depression. They may also advise whether pharmacological treatment may be appropriate.

D1.7 Speech pathologist/therapist

Speech pathologists can be involved in the assessment and management of recurrent aspiration, swallowing and eating difficulties caused by shortness of breath, and dry mouth associated with some pharmaceuticals, age and mouth breathing.

D1.8 Pharmacist

Pharmacists are involved in education about medications and supply of medications. They can help smokers quit by advising about nicotine replacement and can counsel patients requesting over-the-counter salbutamol. They are well placed to monitor for medication problems and complications and suggest solutions (eg, individual dosing dispensers).[226] This is particularly important where multiple comorbid conditions require treatment with multiple medications that have potential interactions, or when confusion exists about timing of medication administration.

D1.9 Dietitian/Nutritionist

Excessive weight-loss is a common problem in patients with end-stage COPD. Conversely, obesity in patients with COPD is associated with sleep apnoea, CO2 retention and cor pulmonale. Dietitians play a central role in managing these problems.

D1.10 Exercise physiologist

D1.11 Non-medical care agencies

Many patients with COPD have difficulties with activities of daily living and may require a range of non-medical support services, including governmental and non-governmental organisations. Availability of services varies between states and between areas within states (eg, urban, rural, remote). Some examples include:

- financial support and organisation of oxygen, CPAP machines, nebulisers, etc;
- Homecare;
- government-supported assistance with activities of daily living (showering, cleaning, shopping, etc);
- home maintenance;
- Meals on Wheels;
- exercise programs; and
- support groups.

D2. Multidisciplinary care plans

> Multidisciplinary care plans and individual self-management plans may help to prevent or manage crises[101] [evidence level III-2]

A multidisciplinary care plan involves documentation of the various medical, paramedical and non-medical services required to keep a patient functioning in the community. Various generic and disease-specific proformas are available (see http://www.lungnet.com.au/copd.html for examples). The care plan may be initiated in the context of a multidisciplinary case conference involving the GP and at least two other health professionals (one of whom is not a doctor).

GPs are remunerated for their involvement in case conferences. This is supported by Extended Primary Care (EPC) item numbers, which vary according to the level of involvement of the GP and the location of the patient. The GP may participate by telephone. A consultant physician is also entitled to claim rebates for organising or participating in case conferences. Further information about item numbers is available at http://www.health.gov.au/epc.

The multidisciplinary care plan may include a component of self-management with appropriate support.

D3. Self-management

> Patients who take appropriate responsibility for their own management may have improved outcomes[102] [evidence level III-1]

A distinction can be made between 'self management' and 'self-management support'. ‘Self-management’ is a normal part of daily living, and involves the actions individuals take for themselves and their families to stay healthy and to care for minor, acute and long-term conditions. ‘Self management support’ is the facility that healthcare and social-care services provide to enable individuals to take better care of themselves. The onus in recent times has been on delivering training for self-management skills to individuals through a range of interventions.[227]

Patients with chronic illness who participate in self-management have better outcomes, including reduced healthcare costs, than those who do not.[101] This study included some people with COPD. In COPD, behavioural education alone is effective, although less effective than integrated pulmonary rehabilitation programs that include an exercise component.[104]

The concept of written action plans for patients with COPD is derived from their success in asthma management indicating doses and medications to take for maintenance therapy and for exacerbations. Instructions for crises are often also included. A systematic review by Turnock et al[228] found that the use of action plans results in an increased ability to recognise and react appropriately to an exacerbation by individuals. However, there was no evidence these behavioural changes alter health-care utilisation.

D3.1 Maintenance therapy

Detailed discussion of the maintenance therapy for COPD appears in **Section O**. In general, the use of drugs in COPD does not involve back-titration, which is a core principle in asthma management. The exception is when oral glucocorticoids have been given for an acute exacerbation. There is at present no evidence for back titration and further clinical trials are required.

D3.2 Exacerbations and crises

Detailed discussion of the management of exacerbations is found in **Section X**.

For severe exacerbations there is evidence for the use of bronchodilators, antibiotics, systemic glucocorticoids and supplemental oxygen (if patients are hypoxaemic). Selected patients may benefit from early intervention with these agents according to a predetermined plan developed by a GP or respiratory specialist. Some patients can be instructed to start using a “crisis medication pack” while awaiting medical review. They may also be instructed to contact a particular member of the multidisciplinary care team as part of their overall care plan.

Controlled trials are required to document the efficacy of self-management plans in patients with stable COPD, but, drawing on the success of asthma action plans, education of patients with COPD in self-management is recommended. Written plans are usually required to complement such interventions (see examples at http://www.lungnet.com.au/content/view/165/164/).

D4. Treat anxiety and depression

> Depression and anxiety are common in COPD and increase the risk of hospitalisation[229, 230] [evidence level III-2)

The strong relationship between anxiety and COPD has long been established.[104] Anxiety symptoms lead to repeated presentations for hospital admission for many patients, at a significant financial cost[231, 232]. Anxiety and mood disturbances can often be exacerbated by respiratory drugs (eg, theophylline and steroids, respectively).

Identifying individuals at risk for clinical anxiety and developing effective interventions for treating, or, ideally, preventing panic disorder in COPD should be priorities. There are many outcome trials showing the effectiveness of cognitive behavioural therapy in treating panic disorder when no respiratory disease is present. Cognitive behavioural therapy should also be an effective intervention for treating patients with COPD-related panic disorder.

Depression is common in patients with chronic illness, and COPD is no exception.[106] This comorbidity has an important role in worsening health related quality of ,life for this patient group, and also contributes to difficulty with smoking cessation. Pharmacological treatment of depression in COPD may be hampered by poor tolerance of side effects such as sedation, which may cause respiratory depression and aggravate sleep disturbances.

In addition to usual clinical assessment, the presence and impact of anxiety and depression may be reliably predicted with several validated questionnaires.

D5. Referral to a support group

Patients who receive education and psychosocial support show greater improvements in more aspects of health- related quality of life than those who receive education with no ongoing support.[104] One way to provide such education and support is through patient support groups. Support groups aim to empower patients with COPD to take a more active role in the management of their healthcare, and thus reduce the psychosocial impact of their disease. One pathway to support groups is through pulmonary rehabilitation programs. Although no direct evaluation of support groups has been published, the likely benefits are summarised in Box 10.

Box 10 : Patient support groups

Typical support group activities

- Regular meetings
- Expert guest speakers on COPD topics
- Telephone calls, hospital and home visits
- Receive and distribute lung health education information
- Special seminars and patient programs
- Social outings
- Rehabilitation assistance and maintenance of exercise
- Social enjoyment

Benefits of support groups

- Reinforce and clarify information learnt from health professionals
- Provide access to new information on lung health
- Share experiences in a caring environment
- Empower patients to be more actively involved in their healthcare through self-management techniques
- Participate in social activities and exercise programs
- Encourage patients to think more positively about their lung disease
- Help carers understand lung disease

COPD = chronic obstructive pulmonary disease.

D6. End-of-life issues

Terminally ill patients with COPD are usually elderly and have already experienced one or more decades of increasingly frustrating functional restriction. Their course is likely to have been punctuated by hospital admissions. They often have several comorbidities and are frequently dependent on the care of others.

Determining prognosis in end-stage COPD is difficult, although guides to shortened survival include an FEV_1 < 25% predicted, weight loss (body mass index below 18), respiratory failure (Paco2 > 50mmHg, or 6.7 kPa), and right heart failure.

The major ethical issues are deciding whether to offer invasive or non-invasive ventilatory support, or, alternatively, to withhold, limit or withdraw such support. These decisions are often complex, but, as in other areas of medicine, they are ultimately constrained by the standard ethical principles of respect for patient autonomy, and ensuring that good and not harm is achieved. Most patients with end-stage COPD wish to participate in end-of-life management decisions and would prefer to do so in a non- acute setting.

In some states the patient's wishes can be given legal force through the use of an enduring power of attorney or advance health directive. Although difficult for the health professional and potentially distressing for the patient, a frank discussion about these often unspoken issues can be beneficial.

Opioids and many anxiolytics depress ventilatory drive and are contraindicated in most patients with COPD. When palliation is warranted, however, their use for the short term relief of dyspnoea could be considered. [evidence level II][164],[165]

D6.1 Palliative care services

Palliative care services provide symptom control and support for patients facing life threatening illness in hospice, hospital and community. Palliative care is not synonymous with terminal care as many patients have uncontrolled symptoms well before their terminal phase. Palliative care is concerned about how patients are living their lives facing terminal illness:

- Symptom control
- Maintenance of independence, physical function and activity
- Support with psychosocial problems
- Support for carers
- Inter-professional communication

The unit of care includes the family or carers and continues into bereavement. Most services operate on a consultancy basis in hospitals and in the community with direct care in a specialised palliative care unit or hospice. The service is available on consultation to support clinicians, carers and patients receiving a palliative approach. Specialist palliative care may be needed to augment or takeover care in complex situations.

X: Manage eXacerbations

An exacerbation is an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD[11]

Acute exacerbations of COPD often require hospital admission for treatment of respiratory failure. A record linkage study in WA[233] demonstrated that the rate of hospital admission for COPD has been declining. The risk of readmission was highest within three months of discharge and more than half of all patients were readmitted within 12 months. About 10% of patients with a primary diagnosis of COPD died either during admission or within the same year. Median survival from first admission was five years in men and eight years in women. The poorest survival was among older patients with recognised emphysema. In one study of more than 1000 patients admitted to several hospitals with an acute exacerbation of severe COPD, about 50% were admitted with a respiratory infection, 25% with congestive cardiac failure, and 30% with no known cause for the exacerbation.[17] A study of 173 patients with COPD reported an average of 1.3 (range 0–9.6) exacerbations annually. An ecological study of hospital admissions for COPD in Victoria found higher rates of admission in rural and remote areas with greater socioeconomic disadvantage and higher rates of smoking. [234]

In patients with COPD the normally sterile lower airway is frequently colonised by Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis. While the number of organisms may increase during exacerbations of COPD, the role of bacterial infection is controversial.[235-243] Exacerbations can also be caused by viral infection[244] and by non- infectious causes, such as left ventricular failure, pulmonary embolus, and other factors, such as air pollution.[245] Chest trauma and inappropriate use of sedatives can lead to sputum retention and hypoventilation.

Early diagnosis and treatment may prevent admission[246] [evidence level III-2]

Early diagnosis and prompt management of exacerbations of COPD may prevent progressive functional deterioration and reduce hospital admissions.[101],[247] Education of the patient, carers, other support people and family may aid in the early detection of exacerbations. A self-management plan developed in conjunction with the patient's GP and specialist to indicate how to step-up treatment may be useful (see examples at http://www.lungnet.com.au/copd.html). This plan might indicate which medications to take, including antibiotics and oral glucocorticoids. The plan should also require patients to contact their GPs or community nurses to allow rapid assessment (see **section D**).

X1. Home management

Multidisciplinary care may assist home management[101],[247],[248],[249] [evidence level II]

The shortage of hospital beds, especially in winter, has prompted interest in home care for management of COPD exacerbations, with involvement of multidisciplinary teams assisting GPs. Economic studies of such programs have shown mixed results.[101],[247],[248],[249] Up to a quarter of carefully selected patients presenting to hospital emergency departments with acute exacerbations of COPD can be safely and successfully treated at home with support from respiratory nurses. A systematic review of 7 RCTs found no significant differences in readmission rates or mortality, but 'Hospital at Home' schemes were preferred by patients and carers[250] [evidence level I]. However, further research is needed because the studies reviewed were small and trialed different interventions.

A recent randomised controlled trial from Italy assigned 104 elderly patients with acute exacerbations of COPD to a general medical ward or hospital in the home.[251] Patients managed at home had a longer mean length of stay, but there was a significantly reduced risk of readmission over the following 6 months. Only those managed at home demonstrated improvements in depression and quality of life [evidence level II]. It is not clear whether this system could be successfully applied in Australia, as the lengths of stay were longer and readmission rates were higher than observed here.

X2. COPD acute exacerbation plan

X2.1 Confirm exacerbation and categorise severity

Assessment of severity of the exacerbation includes a medical history, examination, spirometry and, in severe cases (FEV_1 < 40% predicted), blood gas measurements, chest x- rays and electrocardiography.

Patients should be provided with and bring a summary of their medical problems and treatment (eg, a personal health record). If available, results of previous stable lung function tests and arterial blood gas measurements are invaluable for comparison.

- **Spirometry:** Unless confused or comatose, even the sickest of patients can perform an FEV_1 manoeuvre. An FEV_1 less than 1.0 L (or < 40% predicted) is usually indicative of a severe exacerbation in patients with moderate COPD. For patients with stable levels below these values (ie, severe COPD), the most important signs of a severe exacerbation will be worsening hypoxaemia, acute respiratory acidosis (carbon dioxide retention), or both.
- **Arterial blood gases:** Arterial blood gas levels should be measured if the FEV_1 is less than 1.0 L or less than 40% predicted, or if there is respiratory failure or cor pulmonale. Values obtained while breathing room air are the most useful for assessing ventilation–perfusion inequality. A Pao2 less than 60 mmHg (8 kPa) indicates respiratory failure, while a Paco2 greater than 45 mmHg indicates ventilatory failure.Respiratory acidosis indicates acute respiratory failure warranting consideration for assisted ventilation.
- **Chest x-ray and electrocardiogram:** These help to identify alternative diagnoses and complications, such as pulmonary oedema, pneumothorax, pneumonia, empyema, arrhythmias, myocardial ischaemia and others.

X2.2 Optimise treatment

An acute exacerbation of COPD may involve an increase in airflow limitation, excess sputum production, airway inflammation, infection, hypoxia, hypercarbia and acidosis. Treatment is directed at each of these problems.

- **Bronchodilators:** Inhaled beta-agonist (eg, salbutamol, 400–800mcg; terbutaline, 500–100mcg) and anticholinergic agent (ipratropium, 80mcg) can be given by pressurised metered dose inhaler and spacer, or by jet nebulisation (salubutamol, 2.5–5 mg; terbutaline, 5 mg; ipratropium, 500mcg). The dose **interval is titrated to the response and can range from hourly to six-hourly.**
- Glucocorticoids: Oral glucocorticoids hasten resolution and reduce the likelihood of relapse. Up to two weeks' therapy with prednisolone (40–50 mg daily) is adequate. Longer courses add no further benefit and have a higher risk of side effects.
- **Antibiotics:** Antibiotics are given for purulent sputum to cover for typical and atypical organisms.
- **Controlled oxygen therapy:** This is indicated in patients with hypoxia, with the aim of improving oxygen saturation to over 90% (PaO_2 > 50 mmHg, or 6.7 kPa). Use nasal prongs at 0.5–2.0 L/minute or a venturi mask at 24% or 28%. Minimise excessive oxygen administration, which can worsen hypercapnia.
- **Ventilatory assistance:** This is indicated for increasing hypercapnia and acidosis. Non-invasive positive pressure ventilation by means of a mask is the preferred method.

X2.2.1 Inhaled bronchodilators for treatment of exacerbations

> Inhaled bronchodilators are effective treatments for acute exacerbations[7],[207],[206],[252-254] [evidence level I]

In exacerbations of COPD, the immediate bronchodilator effect is small, but may result in significant improvement in clinical symptoms in patients with severe obstruction.

Studies of acute airflow limitation in asthma indicate that beta-agonists are as effectively delivered by metered dose inhaler and spacer as by nebuliser.[255] The applicability of this evidence to patients with COPD is unknown. An adequate dose should be used. The dose equivalent to 5 mg of salbutamol delivered by nebuliser is 8–10 puffs of 100mcg salbutamol by metered dose inhaler and spacer. Airflow in the nebuliser should be 6 L per minute or higher to achieve an aerosol. Avoid using high- flow oxygen, which may worsen carbon dioxide retention. High doses of beta-agonists may induce hypokalaemia and predispose to cardiac arrhythmias.

Few studies have examined the use of ipratropium bromide in acute exacerbations of COPD.[253],[254] One study which compared the effectiveness of ipratropium bromide with a beta-agonist showed that each drug produced a small but significant improvement in pulmonary function.[253] Inhaled ipratropium bromide also produced a small but significant increase in Pao2 (average, 6 mmHg, or 0.8 kPa) within 30 minutes of its delivery.

Hospital management of a severe exacerbation usually includes nebulised beta-agonist bronchodilator (eg, salbutamol, terbutaline), given continuously in extremely unwell patients and intermittently in others. This will usually be delivered by means of high flow air. An anticholinergic agent (ipratropium bromide) may be delivered together with the nebulised beta-agonist in patients with severe exacerbations (triage categories 1 and 2) or when response to beta-agonists alone is poor. However, a systematic review[256] that included four randomised controlled trials did not demonstrate any additional benefit on FEV_1 of the combination of an

anticholinergic compared with beta2-agonists alone. [evidence level I] Nebulised medications can also be administered through the assisted ventilation circuit if required.[254]

The mode of delivery should be changed to a metered dose inhaler with a spacer device or a dry powder inhaler within 24 hours of the initial dose of nebulised bronchodilator, unless the patient remains severely ill.[257],[258]

The use of methylxanthines (oral theophylline and IV aminophylline) in the management of acute exacerbations of COPD has diminished because of their potential for toxicity.[259-263] Methylxanthines can also provoke a number of arrythmias including multifocal atrial tachycardia.[36] A systematic review of four Randomised Controlled Trials found a transient increase of 101ml in FEV_1 after three days and a 4-6 fold increased risk of nausea and vomiting[264] [evidence level I]. The routine use of aminophylline is not recommended for non-acidotic acute exacerbations[265] [evidence level II].

X2.2.2 Systemic glucocorticoids for treatment of exacerbations

> Systemic glucocorticoids reduce the severity of and shorten recovery from acute exacerbations.[266-268] [evidence level I]

A randomised controlled trial of systemic glucocorticoids for acute exacerbations of COPD showed a moderate improvement in clinical outcomes.[267] Maximum improvement was gained within two weeks of therapy, and prolonging the course of treatment thereafter did not result in further benefit. An important side effect was hyperglycaemia, often sufficiently severe to warrant treatment. Blood glucose levels should be monitored. Oral or parenteral glucocorticoids are recommended for treating acute exacerbations of COPD [evidence level I]. The optimal dose has not been established, but 30–50 mg prednisolone daily is sufficient for most patients. If intravenous therapy was commenced, this should be changed to oral therapy within 48 hours. An updated systematic review of systemic glucocorticoids for acute exacerbations showed that it would have been necessary to treat nine patients (95% CI 6 to 14) with systemic glucocorticoids to avoid one treatment failure in this time period. [269] Overall, one extra adverse effect occurred for every six people treated (95% CI 4 to 10).

The continued use of inhaled glucocorticoids and the administration technique should be reviewed. At discharge, therapy with oral prednisolone (25–37.5 mg daily) may be continued but the optimal duration is unknown. Tapering of glucocorticoid therapy is not necessary after short-term administration. However, patients who have taken glucocorticoids for more than three consecutive weeks may have adrenal suppression,[267],[268] and their glucocorticoid therapy should not be ceased abruptly.

Patients on long-term oral steroid therapy (> 7.5 mg prednisolone daily for more than 6 months) are at risk of developing osteoporosis. Prevention and treatment of steroid-induced osteoporosis should be considered.

X2.2.3 Antibiotics for treatment of exacerbations

> Exacerbations with clinical signs of infection (increased volume and change in colour of sputum and/or fever, leukocytosis) benefit from antibiotic therapy[200],[201],[244, 270, 271][evidence level II]

Bacterial infection may have either a primary or secondary role in about 50% of exacerbations of COPD.[235],[238],[243],[271] Haemophilus influenzae, Streptococcous pneumoniae and Moraxella catarrhalis are most commonly involved.[235],[237],[242] Mycoplasma pneumoniae and Chlamydia pneumoniae are seen relatively frequently.[235],[241] As lung function deteriorates (FEV_1 < 35%), Pseudomonas aeruginosa and Staphylococcus aureus are often encountered.[235],[237],[243]

Two systematic reviews have found similar benefits for antibiotic treatment over placebo in severe acute exacerbations requiring hospitalisation, despite including different studies. Ram et al[272], including mostly hospital-based studies, found a significant decrease in mortality (RR 0.23, 95% CI 0.10 to 0.52) with a NNT of 8 (95% CI 6 to 17). Puhan et al[273] also found a decrease in mortality of their sub-group analysis of severe exacerbations requiring hospitalisation (OR 0.20, 95% CI 0.06 to 0.62) with a NNT of 14 (95% CI 12 to 30). Both systematic reviews also found a significant decrease in treatment failure. Although Puhan did not combine the results of adverse drug effects due to heterogeneity, Ram found antibiotic treatment increased adverse events, most notably diarrhoea (RR 2.86, 95% CI 1.06 to 7.76) with a NNH of 20 (95% CI 10 to 100). The effect of antibiotics in the general practice setting is unclear. Puhan found no significant benefit for treatment failure in mild and moderate exacerbations treated outside the hospital setting (OR 1.09, 95% CI 0.75 to 1.59).

A systematic review of RCTs has confirmed the overall benefit of antibiotics given for at least five days in acute exacerbations (although most of the data is from the hospital setting).[272] Antibiotics for increased cough and sputum purulence decreased mortality, treatment failure and end of treatment sputum purulence at a cost of an increased risk of diarrhoea. A significant decrease in mortality (RR 0.23; 95% CI 0.10 to 0.52) was found, meaning 8 (95% CI 6 to 17) people needed antibiotic treatment to prevent one death. Treatment increased adverse events, most notably diarrhoea (RR 2.86; 95% CI 1.06 to 7.76), meaning antibiotic treatment in 20 (95% CI 10 to 100) people would result in one additional episode of diarrhoea. Unfortunately, these data are limited by participant numbers and setting, the majority of studies being performed in the hospital setting. Generalisability, especially to the primary care setting where most exacerbations are seen, is unclear.

El Moussaoui et al[274] conducted a systematic review of 21 randomised controlled trials of antibiotics in acute exacerbations of chronic bronchitis and COPD. There were similar rates of clinical or bacteriological cure with short courses (≤ 5 days) and longer courses of antibiotics [evidence level I]. However the antibiotics evaluated were late generation cephalosporins, macrolides and fluoroquinolones, which are not those recommended in Australia.

Therapeutic guidelines: antibiotic[275] recommend the use of oral agents such as doxycycline or amoxycillin (alternatively, erythromycin or roxithromycin). If patients do not respond, or if resistant organisms are suspected, amoxycillin–clavulanate should be prescribed. If pneumonia, pseudomonas or staphylococci is suspected, appropriate antibiotics should be used.

Typically, a course of treatment should be over seven to 10 days. A response is usually seen within three to five days, and a change of antibiotic should be considered if the response is unsatisfactory. If parenteral administration was commenced, oral treatment should be substituted within 72 hours.

Radiologically proven pneumonia in patients with COPD, especially in those who have been frequently hospitalised, may not be restricted to the above organisms. Gram- negative organisms, Legionella spp. and even anaerobic organisms may be responsible. Initial empiric antibiotic therapy should be tailored according to clinical and radiographic criteria.

X3. Refer appropriately to prevent further deterioration ('P')

The risk of death from exacerbations of COPD increases with acute carbon dioxide retention (respiratory acidosis), the presence of significant comorbid conditions (eg, ischaemic heart disease) and complications (eg, pneumonia and empyema). Depending on the nature and severity of the exacerbation, the patient may require urgent specialist review, hospital assessment or admission to a high-dependency or intensive care facility for ventilatory support and appropriate monitoring (see Boxes 11 and 12).

Box 11: Indications for hospitalisation of patients with chronic obstructive pulmonary disease

Marked increase in intensity of symptoms

Patient has acute exacerbation characterised by increased dyspnoea, cough or sputum production, plus one or more of the following:

- Inadequate response to ambulatory management
- Inability to walk between rooms when previously mobile
- Inability to eat or sleep because of dyspnoea
- Cannot manage at home even with home-care resources
- High risk comorbidity condition — pulmonary (eg, pneumonia) or non-pulmonary
- Altered mental status suggestive of hypercapnia
- Worsening hypoxaemia or cor pulmonale
- Newly occurring arrhythmia

Box 12: Indications for non-invasive or invasive ventilation

- Severe dyspnoea that responds inadequately to initial emergency therapy
- Confusion, lethargy or evidence of hypoventilation
- Persistent or worsening hypoxaemia despite supplemental oxygen, worsening hypercapnia (Paco2 > 70 mmHg), or severe or worsening respiratory acidosis (blood pH < 7.3)
- Assisted mechanical ventilation is required.

X3.1 Controlled oxygen delivery

Controlled oxygen delivery (28%, or 0.5–2.0 L/min) is indicated for hypoxaemia[276]

Correction of hypoxaemia to achieve a Pao2 of at least 55 mmHg (7.3 kPa) and an oxygen saturation of 88%–92% is the immediate priority.[7] Where there is evidence of acute respiratory acidosis (or a rise in Paco2), together with signs of increasing respiratory fatigue and/or obtunded conscious state, assisted ventilation should be considered. Early non- invasive positive pressure ventilation (NIPPV) may reduce the need for endotracheal intubation (see below for more detail).

Administering oxygen at an inspired oxygen concentration (fraction of inspired oxygen; Fio2) of 24%–28% by means of a venturi mask is usually sufficient to improve oxygenation in most patients. Nasal cannulas, although more comfortable, deliver a variable concentration of oxygen, but a flow of 0.5–2.0 L per minute is usually sufficient. Gas flow provided through Hudson-type masks is inadequate when patients are tachypnoeic, so these should not be used. Careful monitoring with oximetry and, where hypercapnia is a potential concern, arterial blood gas measurement is required. There is no benefit in trying to obtain Spo2 levels over 92%.

High flow oxygen should be avoided, as it is rarely necessary and may lead to hypoventilation and worsening respiratory acidosis. Patients should be weaned off supplementary oxygen as soon as possible, with none for 24–48 hours before discharge, unless home oxygen is prescribed.

There is currently insufficient evidence to treat acute exacerbations of COPD with Heliox mixture.

X3.2 Non-invasive positive pressure ventilation

Non-invasive positive pressure ventilation is effective for acute hypercapnic ventilatory failure[277][evidence level I]

Ventilatory support with intermittent positive pressure ventilation (IPPV) should be considered in patients with rising Paco2 levels who are unable to ventilate adequately (ie, acute or acute-on-chronic respiratory acidosis).[278-282] This can be achieved non-invasively (by means of a face mask, NIPPV) or invasively through an endotracheal tube.[283],[284]

NIPPV is an effective and safe means of treatment of ventilatory failure. Its use allows preservation of cough, physiological air warming and humidification, and normal swallowing, feeding and speech. Early intervention with NIPPV is suggested when the respiratory rate is less than 30 per minute and blood pH is less than 7.35. An improvement in respiratory rate and pH usually occurs within one hour of starting NIPPV.[278-282] Failure to respond or further deterioration would indicate a need to consider intensive care unit admission (see Box 12 above).

Applying non-invasive ventilation in addition to conventional therapy reduces mortality (Relative Risk 0.5), and the need for intubation (RR 0.4) and its potential complications. NIPPV results in more rapid improvements in respiratory rate, dyspnoea score and blood gas abnormalities than conventional therapy alone. Some studies have also shown an improvement in survival and a reduced length of stay in hospital (Weighted Mean Difference 3.24 days)[277] [evidence level I].

X3.3 Invasive ventilation (intubation)

NIPPV is contraindicated in patients who are unable to protect their airways, are not spontaneously breathing or who have severe facial injury or burns.[284] Relative contraindications (situations where NIPPV may be less effective) include life-threatening refractory hypoxaemia (Pao2 < 60 mmHg, or 8 kPa on 100% inspired oxygen), bronchiectasis with copious secretions, severe pneumonia, and haemodynamic instability. These patients may require intubation. Patients who need mechanical ventilation have an inpatient mortality of up to 37%. A multi-centre Spanish study[285] that followed surviving patients for 6 years found that subsequent mortality was related to age, Acute Physiology And Chronic Health Evaluation (APACHE) score and quality of life. Although quality of life deteriorated over time, 72% of the survivors remained self sufficient [evidence level III-2].

Weaning from invasive ventilation can be facilitated by the use of non-invasive positive pressure ventilation with outcomes which resulted in decreased mortality (RR 0.41) and reduced hospital length of stay (WMD 7.33 days) [286]

The patient's wishes regarding intubation and resuscitation should ideally be documented before an admission for management of respiratory failure. Patients who require ventilatory support during exacerbations of COPD may have impaired control of breathing or apnoeas during sleep, even when well. Therefore, performing a diagnostic sleep study when the patient's condition is stable should be considered. Narcotic analgesics and sedatives should be avoided, as these may worsen ventilatory failure and hasten the need for positive pressure ventilation.

X3.4 Clearance of secretions

Patients who regularly expectorate or those with tenacious sputum may benefit from forced expiratory techniques. If patients produce more than 25 mL sputum per day, or if mucus plugging with lobar atelectasis is present, physiotherapy incorporating the use of postural drainage and associated techniques such as percussion and vibration may help.[112],[201]

X3.5 Develop post-discharge plan and follow-up

The aim is to relieve hypoxaemia and obtain improvement in clinical signs and symptoms.

- ***Clinical examination:*** Reduction in wheeze, accessory muscle use, respiratory rate, distress.
- ***Gas exchange:*** Arterial blood gas levels and/or pulse oximetry levels should be monitored until the patient's condition is stable (Spo2 88%–92%).
- ***Respiratory function testing:*** FEV_1 should be recorded in all patients after recovery from an acute exacerbation.
- ***Discharge planning:*** Discharge planning should be commenced within 24–48 hours of admission.

X3.6 Pulmonary rehabilitation

A pulmonary rehabilitation program that includes supervised exercise training can be initiated immediately following an acute exacerbation. Such a program involves functional exercise capacity, health-related quality of life, and may reduce unplanned hospital admissions and mortality[287] [evidence level I].

X3.7 Discharge planning

> Involving the patient's general practitioner in a case conference and developing a care plan may facilitate early discharge

Discharge planning involves the patient, external lay and professional carers, the multidisciplinary hospital and community team and the patient's regular GP. It should commence on admission and be documented within 24–48 hours (see Box 13). Appropriate patient education and attention to preventive management are likely to reduce the frequency of further acute exacerbations. Assessment of social supports and domestic arrangements are critical in discharge planning. Medicare items support aspects of discharge planning.

A discharge pack, which includes general information about COPD, advice on medication use and written instructions on use of inhalation and oxygen devices, if appropriate, as well as a plan for management of worsening symptoms, should be provided. The GP (and respiratory outreach program, if available) should be notified during the patient's admission. A case conference involving the multidisciplinary team and GP may assist successful transition to the community. Medicare Benefits Schedule Enhanced Primary Care item numbers may be claimed for "participation in a case conference" and "contribution to a care plan" (see **Section D**).

Before discharge, referral to a comprehensive pulmonary rehabilitation program should be considered.

Box 13: Criteria for discharge

Suggested criteria for a patient's readiness for discharge include:

- The patient should be in a clinically stable condition and have had no parenteral therapy for 24 hours
- Inhaled bronchodilators are required less than four-hourly
- Oxygen delivery has ceased for 24 hours (unless home oxygen is indicated)
- If previously able, the patient is ambulating safely and independently, and performing activities of daily living
- The patient is able to eat and sleep without significant episodes of dyspnoea
- The patient or caregiver understands and is able to administer medications

Follow-up and home care arrangements (eg, home oxygen, home-care, Meals on Wheels, community nurse, allied health, GP, specialist) have been completed.

X3.8 Support after discharge

Follow-up at home after discharge from hospital may extend the continuum-of-care process begun within the acute environment, although evidence supporting benefit from nurse-led chronic disease management for people with COPD is absent[288] [evidence level I]. Telephone follow-up may be a way of systematically extending support to patients and increasing their coping strategies at home, but the outcomes of this intervention have not been studied systematically.

An integrated approach involving a discharge plan shared with the primary care team together with access to a case manager through a web-based call centre has been shown to reduce re-admissions for COPD exacerbations compared to usual care[289] (evidence level II). This trial was conducted in Europe and the applicability to other settings is not known.

X3.9 Clinical review and follow-up

There are no randomised clinical trials that have addressed the best method for follow-up.[290] It is recommended that the first review after a hospital admission should be by the GP and within seven days of discharge (Box 14). A decision about the requirement for specialist review should be made at the time of discharge. Follow-up care allows further discussion of self-management plans and future monitoring.[290]

Box 14: Follow-up – initial and subsequent

- Assessment of the patient's coping ability and strategies
- Measurement of FEV_1 and performance status
- Reassessment of medication adherence and techniques with inhalation devices
- Review of vaccination status (influenza and pneumococcal)
- Assessment for long-term oxygen therapy (may require reference to specialist facility)
- Consideration of referral for pulmonary rehabilitation
- Assessment of risk of osteoporosis and management
- Smoking cessation — counsel and/or refer
- Assess nutritional status (frequent small meals reduce dyspnoea)

Appendices

Appendix 1. Use and doses of long-term inhaled bronchodilator and glucocorticoids determined in response trials

Response	Drug	Dose (mcg)	Frequency	Delivery
Improved airway function Improved exercise capacity Reduced breathlessness Improved quality of life	beta-Agonist			
	Salbutamol	200mcg	4-6-hourly	MDI/spacer
	Terbutaline	500mcg	6-8-hourly	DPI
	Salmeterol	50mcg	12-hourly	MDI/DPI
	Formoterol	12mcg	12-hourly	MDI/DPI
	Anticholinergic			
	Ipratropium	40-80mcg	6-8-hourly	MDI/spacer
	Tiotropium	18mcg	24-hourly	DPI
	Glucocorticoid			Inhaled
	Beclomethasone (small particle)	400-800mcg/day		MDI/spacer
	Budesonide	800-1600mcg/day		DPI
	Fluticasone	500-1000mcg/day		MDI/DPI
	Ciclesonide	80-320mcg/day		MDI – spacer not reccommended

MDI=metered dose inhaler. DPI=dry powder inhaler.

Appendix 2. Explanation of inhaler devices

Delivery system	Available products	Considerations
Metered dose inhaler (MDI)	Qvar (beclomethasone 50mcg, 100mcg); Flixotide (fluticasone 50mcg, 125mcg, 250mcg); Atrovent (ipratropium bromide 20mcg); Ventolin, Asmol, Airomir, Epaq (salbutamol 100mcg); Serevent (salmeterol 25mcg); Alvesco (ciclesonide 80mcg, 160mcg)	MDIs should be used with a spacer device, as some people have difficulty coordinating the release of medication with inhalation.
Spacers	Aerochamber Breath-A-Tech Fisonair Nebuhaler Volumatic	The spacer chamber acts as a reservoir for the aerosol released from an MDI. The patient can then inhale from this chamber without having to coordinate the release of the medication. Use of spacers with inhaled glucocorticoids reduces side effects of oral candidiasis and hoarseness, as well as optimising medication delivery. MDI with spacer is as effective as a nebuliser if an equivalent dose is taken; 10-15 puffs of 100mcg salbutamol MDI via a spacer is therapeutically equivalent to a 5mg salbutamol nebule. Spacers are cheap, portable, easily cleaned and maintained, do not require electricity and are simple and quick to use. A small volume spacer is preferable when the vital capacity is less than 1.5L.
Autohaler	Airomir (salbutamol 100mcg); Qvar (beclomethasone 50mcg, 100mcg)	Breath-activated MDI containing 200 doses of medication. Use can improve lung deposition in patients with poor MDI inhaler technique. As the patient starts a slow, deep breath through the mouthpiece, a flap valve is triggered and the dose automatically releases.
Dry powder inhalers (DPI)		
Accuhaler	Serevent (salmeterol 50mcg); Flixotide (fluticasone 100mcg, 250mcg, 500mcg); Seretide (salmeterol 50mcg and fluticasone 100mcg, 250mcg, 500mcg)	Breath-activated multi-dose DPI containing 60 individually sealed doses. A dose counter shows the number of doses remaining. It gives accurate and consistent drug delivery over a range of inspiratory flow rates (30-120L/minute). Lactose powder is combined with the active medication for patients to taste and reassure them that they have inhaled a dose.
Aerolizer	Foradile (formoterol 12mcg)	Breath-activated single-dose powder inhaler that comes with a sheet of 60 capsules in push-out foil sheet. One capsule is loaded into the inhaler and pierced before inhaling. Gives consistent drug delivery over a range of inspiratory flow rates.
Turbuhaler	Bricanyl (terbutaline 500mcg); Pulmicort (budesonide 100mcg, 200mcg, 400mcg); Oxis (formoterol 6mcg, 12mcg); Symbicort (formoterol 6mcg and budesonide 200mcg, formoterol 12mcg and budesonide 400mcg)	Breath-activated multi-dose inhaler, containing 60 (Oxis, Symbicort) or 200 (Pulmicort, Bricanyl) doses; ensures delivery without the need to coordinate inspiration with drug release. Dose delivery is halved if the patient cannot produce inspiratory flow above 30L/min. Very few patients with COPD cannot produce a rate of >60L/min. Produces very fine powder, so patients often don't taste anything. Dose indicator shows when there are 20 doses remaining, and then when the inhaler is empty (it contains a drying agent that can be heard when the inhaler is shaken, which can be misinterpreted as available medication).
HandiHaler	Spiriva (tiotropium 18mcg)	Breath-activated dry powder inhaler. A capsule containing tiotropium is dropped into the HandiHaler, and pierced by pressing a button. The patient then inhales through the mouthpiece for effective drug delivery. Studies have shown that patients with a wide range of disease severity are able to generate sufficient inspiratory airflow (as low as 20L/min) to evacuate the powder from the capsule.

Nebulisers	Most nebulisers are electric. Some ultrasonic nebulisers are battery operated. These models are not heavy duty, but are ideal for travelling. There are also 12-volt pumps that plug into a car cigarette lighter. Use of inhaled glucocorticoids requires a high-flow, heavy- duty pump.	Glucocorticoid or ipratropium bromide aerosol should not be allowed to enter the eyes to avoid the risk of side effects such as glaucoma or urinary outlet obstruction. Patients should be advised to wipe their face dry after using the nebuliser to remove medication from the skin. Ipratropium can be combined with beta-agonist, but not with glucocorticoid.
The products listed are not all subsidised under the Pharmaceutical Benefits Scheme for use in COPD.		

Appendix 3. Long term oxygen therapy[291]

Initiating oxygen therapy

- Before introducing oxygen therapy, ensure optimal treatment of the pulmonary disorder while monitoring improvement with objective tests such as FEV_1 and FVC. Treatment may include maximum therapy for airway obstruction, attention to nutrition and bodyweight, an exercise rehabilitation program, control of infection, and treatment of cor pulmonale.
- In patients selected for oxygen therapy, assess the adequacy of relief of hypoxaemia (PaO_2 > 60 mmHg, or 8 kPa; Spo2 > 90%) and/or improvement in exercise capacity or nocturnal arterial oxygen saturation while using a practical oxygen delivery system.

What the patient needs to know

- Patients receiving oxygen therapy in the home, and their carers, should have the use clearly explained. That is, hours of use and flow rate, and any need to vary flow rates at given times. The equipment and its care, including how to obtain servicing or replacements, needs to be explained. The dangers of open flames (especially cigarettes, gas heaters and cookers) need to be emphasised.
- Flow should be set at the lowest rate needed to maintain a resting PaO_2 of 60 mmHg (8kPa) or Spo2 > 88%. For patients with COPD, 0.5–2.0 L/min is usually sufficient. Flow rate should be increased by 1 L/min during exercise.
- Humidifiers are generally not needed at oxygen flow rates below 4 L/min.
- Extrasoft nasal prongs are recommended for continuous oxygen use, but may become uncomfortable at flow rates over 2–3 L/min and in the long term. Facemasks may be preferred for at least some of the time, although there are dangers of rebreathing exhaled CO_2 at flow rates below 4 L/min.
- In some patients needing 24-hour oxygen therapy, transtracheal delivery systems may have advantages.

Review

- Reassess 4–8 weeks after starting continuous or nocturnal oxygen therapy, both clinically and by measurement of PaO_2 and $PaCO_2$, with and without supplementary oxygen. A decision can then be made as to whether the treatment has been properly applied and whether it should be continued or abandoned.
- Patients on intermittent oxygen therapy should also be reassessed periodically. The review can be undertaken by appropriately trained staff using a pulse oximeter to confirm hypoxaemia (SpO_2 < 88%) at rest or during daily activities. They should also check compliance with therapy and smoking status.
- Review at least annually or more often according to the clinical situation.

Dangers

- Supplementary oxygen in patients with increased arterial PaO_2 may depress ventilation, increase physiological dead space, and further increase arterial PaO_2. This is suggested by the development of somnolence, headache and disorientation.
- In long-term oxygen therapy, the increase in arterial PaO_2 is usually small and well tolerated. However, serious hypercapnia may occasionally develop, making continued oxygen therapy impractical. Risk appears greater during acute exacerbations of disease or if the flow of oxygen is increased inappropriately.
- Sedatives (particularly benzodiazepines), narcotics, alcohol and other drugs that impair the central regulation of breathing should not be used in patients with hypercapnia receiving oxygen therapy.

Choosing the right method

Domiciliary oxygen therapy can be delivered by three systems:

- ***Cylinders:*** These contain compressed oxygen gas and deliver 100% oxygen at the outlet. Portable lightweight cylinders are available. Electronic conservation devices trigger oxygen supply on demand, resulting in up to fourfold reduction in oxygen consumption. Reservoir-style conservers are a cost-effective alternative.
- ***Oxygen concentrators:*** These extract the nitrogen from room air by means of molecular sieves, delivering 90%–95% oxygen at a flow rate of 2 L/min. The percentage falls to about 78% oxygen at a flow of 5 L/min, depending on the model. All units currently available in Australia are imported. A back-up standard D-size oxygen cylinder may be added in case of concentrator breakdown or power failure, but adds to the cost and is rarely necessary. Users may claim a rebate on their electricity account.
- ***Liquid oxygen systems:*** These systems conserve space by storing oxygen in liquid form. The oxygen is delivered through coils, where it vaporises. Two tanks are needed: a large storage tank, which is filled by the supplier as required (eg, one unit has a 25 800 L gaseous capacity, equivalent to seven E-size cylinders), and a portable unit is filled from the larger tank for ambulatory use.

The prescription should always specify:

- the source of supplemental oxygen (gas or liquid);
- method of delivery;
- duration of use; and
- flow rate at rest, during exercise and during sleep.

There is no significant difference in the quality of oxygen delivery among the above methods. However:

- Concentrators are cheaper than cylinders if use is equivalent to or more than three E-size cylinders per month.
- Concentrators can be wheeled around the home but are heavy (about 21–26 kg) and are difficult to move up stairs and in and out of cars.
- Concentrators cannot be used for nebulisation, as the pressure delivered is too low (35–63 kPa, compared with 140 kPa for nebuliser pumps).
- If the anticipated need is for longer than three years, it is cheaper to buy than to rent a unit. The units usually have a five-year guarantee. However, public funding is available for pensioners and Health Care Card holders, subject to means testing.

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