

# The COPDX Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2014

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These guidelines have been developed and revised by Lung Foundation Australia and the Thoracic Society of Australia and New Zealand as part of a national COPD program.

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## Foreword

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is very common and a major cause of disability, hospital admission and premature death.

The criteria used to determine the presence of COPD vary and are responsible for differing estimates of prevalence. Separate studies from both Australia and New Zealand showed that 14% of Australians and 14.2% of New Zealanders aged 40 years or more had some degree of COPD using Global Initiative for Obstructive Lung Disease (GOLD) criteria. (Toelle et al., 2013) (Shirtcliffe et al., 2012) However using a different definition to identify cases, the prevalence of COPD was 9% in people aged 40 years or more. (Shirtcliffe et al., 2007) As the population ages it is likely more people will be affected by COPD.

The Australian Institute of Health and Welfare estimated that COPD was the fifth greatest contributor to the overall burden of disease, accounting for 3.6% of disability-adjusted life years (DALY) in 2003. (Australian Institute of Health and Welfare, 2008) Chronic obstructive pulmonary disease ranks sixth among the common causes of death in Australian men and sixth in women. (Australian Institute of Health and Welfare, 2008) In New Zealand, it ranks fifth in both men and women (Ministry of Health, 2010) The death rate from COPD among Indigenous Australians is five times that for non-Indigenous Australians. In New Zealand, the age standardised death rate for Maori (46.1 per 100,000) is more than double that for non-Maori (18.1 per 100,000). The disease costs the Australian community an estimated \$8.8 billion annually in financial costs, including health and hospital costs, lost productivity, premature death and a low rate of employment. (Access Economics Pty Limited for The Australian Lung Foundation, 2008)

Chronic obstructive pulmonary disease is commonly associated with other chronic diseases including heart disease, lung cancer, stroke, pneumonia and depression.

Smoking is the most important risk factor for COPD. In 2011/12, 18.2% of Australian males and 14.4% of Australian females over the age of 18 years smoked daily. (Australian Bureau of Statistics, 2012) Smoking-related diseases have increased substantially in women, and death rates from COPD in women are expected to rise accordingly. Smoking is a leading cause of healthy years lost by Indigenous people both in Australia and New Zealand.

As with any chronic disease, optimum management of COPD requires health system reform in order that both anticipatory care (e.g. developing self-management capacity) and acute care (e.g. treating exacerbations) are planned for. It is beyond the scope of these guidelines to address all the health system reforms that may be required for chronic disease care. Such reforms will require changes of approach in micro-systems (e.g. a general practice or community physiotherapy service), in organisational structures and systems that coordinate care in regions (e.g. Medicare Locals; Primary Health Care Organisations, Local Hospital Networks) as well as in national and state health policy making institutions.

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 seeks to summarise current evidence around optimal management of people with COPD. It is intended to be a decision support aid for general practitioners, other primary health care clinicians, hospital based clinicians and specialists working in respiratory health. Published evidence is systematically searched for, identified, and reviewed on a regular basis. The COPD Guidelines Evaluation Committee meets four times a year and determines whether the reviewed evidence needs incorporation into the guideline.

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

- C**onfirm diagnosis,
- O**ptimise function,
- P**revent deterioration,
- D**evelop a self-management plan and manage
- eX**acerbations.

Professor Nicholas Glasgow (on behalf of the COPD Evaluation Committee)  
December 2011

## The COPD guidelines

THESE GUIDELINES are the outcome of a joint project of the Thoracic Society of Australia and New Zealand and Lung Foundation Australia. 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 Lung Foundation Australia, 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. (National Health and Medical Research Council, 1998) The Committee agreed to use the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Report (NHLBI/WHO Workshop Report, April 2001) 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> (now [www.lungfoundation.com.au](http://www.lungfoundation.com.au)) 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.

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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). (NHLBI/WHO Workshop Report, April 2001) The NHLBI scheme is shown in **Box 1**. For comparison, the National Health and Medical Research Council (NHMRC) (National Health and Medical Research Council, 1998) 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.

## Executive Summary of the COPDX guidelines

C: Confirm diagnosis and assess severity	Evidence level
<ul style="list-style-type: none"> <li>Smoking is the most important risk factor in the development of COPD</li> </ul>	I
<ul style="list-style-type: none"> <li>Consider COPD in all smokers and ex-smokers over the age of 35 years</li> </ul>	II
<ul style="list-style-type: none"> <li>The diagnosis of COPD rests on the demonstration of airflow limitation which is not fully reversible</li> </ul>	II
<ul style="list-style-type: none"> <li>It is important in general practice settings to obtain accurate spirometric assessment</li> </ul>	III-3
<ul style="list-style-type: none"> <li>If airflow limitation is fully or substantially reversible (FEV<sub>1</sub> response to bronchodilator &gt;400ml), the patient should be treated as for asthma</li> </ul>	
<ul style="list-style-type: none"> <li>Consider COPD in patients with other smoking-related diseases</li> </ul>	I
O: Optimise function	
<ul style="list-style-type: none"> <li>Inhaled bronchodilators provide symptom relief and may increase exercise capacity</li> </ul>	I
<ul style="list-style-type: none"> <li>Long term use of systemic corticosteroids is not recommended</li> </ul>	I
<ul style="list-style-type: none"> <li>Inhaled corticosteroids should be considered in patients with moderate to severe COPD and frequent exacerbations</li> </ul>	I
<ul style="list-style-type: none"> <li>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</li> </ul>	I
<ul style="list-style-type: none"> <li>Pulmonary rehabilitation reduces hospitalisation and has been shown to be cost-effective</li> </ul>	II
<ul style="list-style-type: none"> <li>Prevent or treat osteoporosis</li> </ul>	
<ul style="list-style-type: none"> <li>Identify and treat hypoxaemia and pulmonary hypertension</li> </ul>	I
<ul style="list-style-type: none"> <li>In selected patients, a surgical approach may be considered for symptom relief</li> </ul>	III-2
P: Prevent deterioration	
<ul style="list-style-type: none"> <li>Smoking cessation reduces the rate of decline of lung function</li> </ul>	I
<ul style="list-style-type: none"> <li>Treatment of nicotine dependence is effective and should be offered to smokers in addition to counselling</li> </ul>	I
<ul style="list-style-type: none"> <li>Influenza immunisation reduces the risk of exacerbations, hospitalisation and death</li> </ul>	I
<ul style="list-style-type: none"> <li>Mucolytics may reduce the frequency and duration of exacerbations</li> </ul>	II
<ul style="list-style-type: none"> <li>Long-term oxygen therapy (&gt;15h/day) prolongs life in hypoxaemic patients (PaO<sub>2</sub>&lt;55mmHg, or 7.3kPa)</li> </ul>	I
D: Develop support network and self-management plan	
<ul style="list-style-type: none"> <li>COPD imposes handicaps which affect both patients and carers</li> </ul>	II
<ul style="list-style-type: none"> <li>Enhancing quality of life and reducing handicap requires a support team</li> </ul>	
<ul style="list-style-type: none"> <li>Patients and their family/friends should be actively involved in a therapeutic partnership with a range of health professionals</li> </ul>	II
<ul style="list-style-type: none"> <li>Multidisciplinary care plans and individual self-management plans may help to prevent or manage crises</li> </ul>	III-2
<ul style="list-style-type: none"> <li>Patients who take appropriate responsibility for their own management may have improved outcomes</li> </ul>	III-1
<ul style="list-style-type: none"> <li>Anxious and depressive symptoms and disorders are common comorbidities in people with COPD</li> </ul>	I
X: Manage eXacerbations	
<ul style="list-style-type: none"> <li>An exacerbation is an event in the natural course of the disease characterised 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</li> </ul>	
<ul style="list-style-type: none"> <li>Early diagnosis and treatment may prevent admission</li> </ul>	III-2
<ul style="list-style-type: none"> <li>Multidisciplinary care may assist home management</li> </ul>	II
<ul style="list-style-type: none"> <li>Inhaled bronchodilators are effective treatments for acute exacerbations</li> </ul>	I
<ul style="list-style-type: none"> <li>Systemic corticosteroids reduce the severity of and shorten recovery from acute exacerbations</li> </ul>	I
<ul style="list-style-type: none"> <li>Exacerbations with clinical signs of infection (increased volume and change in colour of sputum and/or fever, leukocytosis) benefit from antibiotic therapy</li> </ul>	II
<ul style="list-style-type: none"> <li>Controlled oxygen delivery (28%, or 0.5-2.0L/min) is indicated for hypoxaemia</li> </ul>	
<ul style="list-style-type: none"> <li>Non-invasive positive pressure ventilation is effective for acute hypercapnic ventilatory failure</li> </ul>	I
<ul style="list-style-type: none"> <li>Involving the patient's general practitioner in a case conference and developing a care plan may facilitate early discharge</li> </ul>	

## C: Confirm diagnosis and assess severity

Smoking is the most important risk factor in the development of COPD (Fletcher and Peto, 1977), (Burrows et al., 1977) [evidence level I]

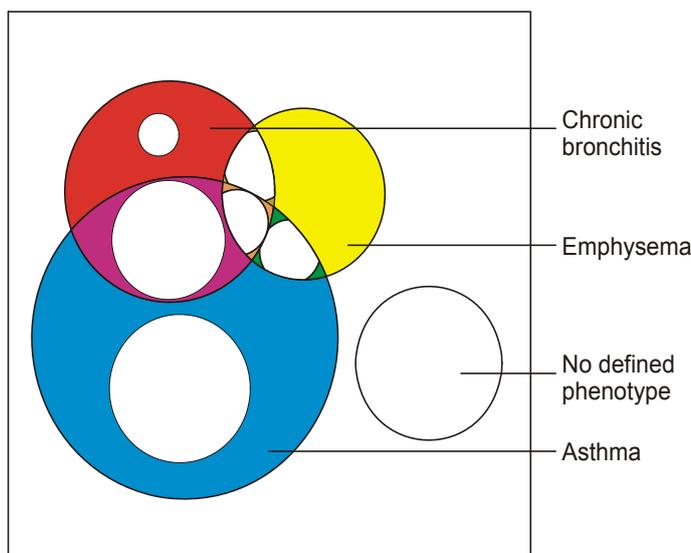
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation which is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases (Global Initiative for Chronic Obstructive Lung Disease). 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. (NHLBI/WHO Workshop Report, April 2001) 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 **Figure 1**. This proportional Venn diagram presents data from the Wellington Respiratory Survey which recruited subjects over the age of 50 and invited them to have detailed lung function testing and chest CT scans. (Marsh et al., 2008) It can be seen that almost all patients with both chronic bronchitis and emphysema meet the GOLD definition of COPD, as do most with both chronic bronchitis and asthma. Patients with chronic bronchiolitis, bronchiectasis and cystic fibrosis may also present with similar symptoms and partially reversible airflow limitation.

**Figure 1: COPD Phenotypes**



The diagram (reproduced from Thorax 2008;63:761-7 with permission from the BMJ Publishing Group) presents the different phenotypes within the Wellington Respiratory Survey study population. The large black rectangle represents the full study group. The clear circles within each coloured area represent the proportion of subjects with COPD (post-bronchodilator forced expiratory volume in 1 s/forced vital capacity ( $FEV_1/FVC$ ), 0.7). The isolated clear circle represents subjects with COPD who did not have an additional defined phenotype of asthma, chronic bronchitis or emphysema.

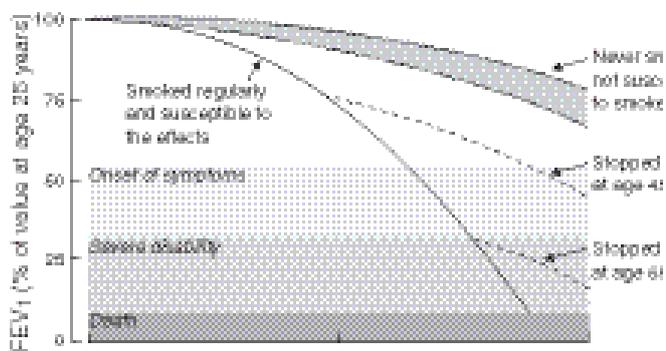
## C1. Aetiology and natural history

Cigarette smoking is the most important cause of COPD.(Fletcher and Peto, 1977),(Burrows et al., 1977) There is a close relationship between the amount of tobacco smoked and the rate of decline in forced expiratory flow in one second (FEV<sub>1</sub>), although individuals vary greatly in susceptibility.(Fletcher and Peto, 1977) Around half of all smokers develop some airflow limitation, and 15%–20% will develop clinically significant disability.(Fletcher and Peto, 1977) 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<sub>1</sub> of 25–100mL/year.(Fletcher and Peto, 1977) 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.(Fletcher and Peto, 1977)

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 **Figure 2**.

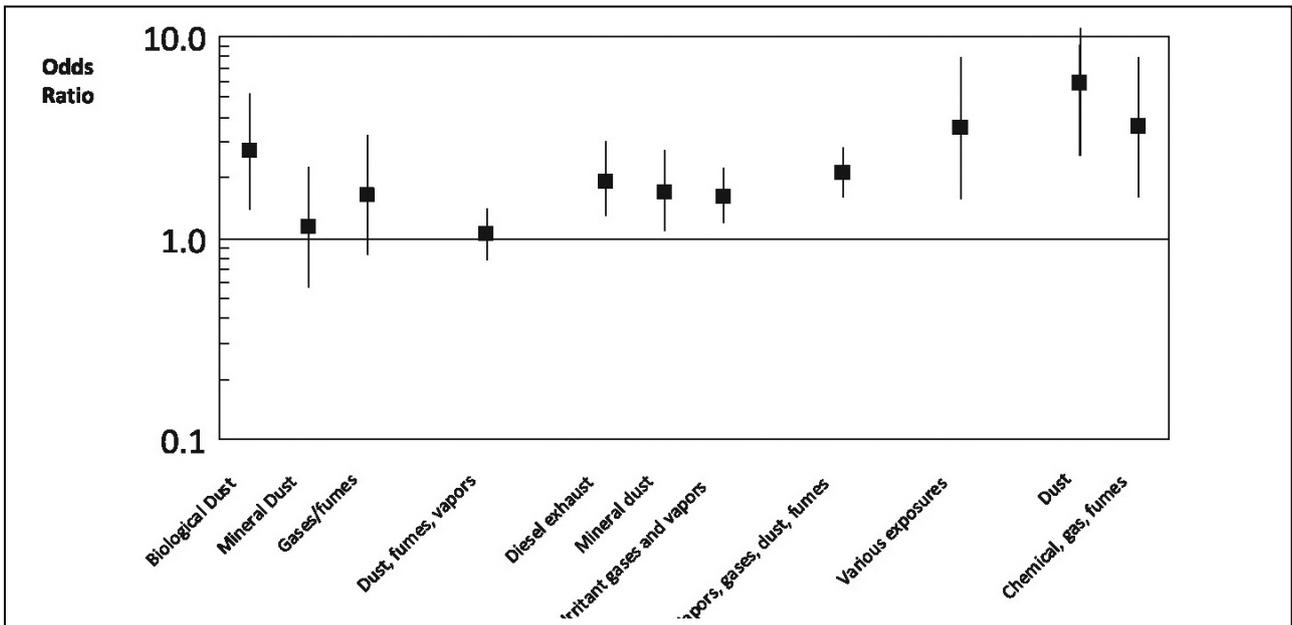
**Figure 2: Time-course of chronic obstructive pulmonary disease (COPD)(Fletcher and Peto, 1977)**



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<sub>1</sub>) 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<sub>1</sub> 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(Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2006) (see **Box 2** below adapted from GOLD 2006). COPD almost always arises from a gene environment interaction. The best characterised genetic predisposition is alpha<sub>1</sub> 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(Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2006) and oxidative stress in the lung. Occupational dust exposure might be responsible for 20 – 30% of COPD. This has long been recognised in coal miners(Santo Tomas, 2011), but biological dust has also been identified as a risk factor, particularly in women.(Matheson et al., 2005) Non-smoking women involved in the spinning, weaving and knitting of cotton or silk have an increased risk of death from COPD.(Cui et al., 2011) Biological dust exposure is also associated with chronic sputum production, dyspnoea and work inactivity in male patients.(Rodriguez et al., 2008) Livestock farmers are also at increased risk of developing chronic bronchitis and COPD (Eduard et al 2009). Dairy farmers have increased wheeze and morning phle.g.m and increased rate of decline in FEV<sub>1</sub> compared to controls. These effects appear to be associated more with exposure to animal feed than handling hay or straw(Thaon et al., 2011). Each year of exposure to diesel exhaust increases the risk of dying from COPD by 2.5%.(Hart et al., 2009) An analysis of a Swiss cohort of 4,267 subjects without asthma found that COPD was associated with high occupational exposures to mineral, biological dusts, vapours/fumes, vapours, gases, dust or fumes (VGDF). The findings were clearer in non-smokers and those without chronic bronchitis(Mehta et al., 2012) [evidence level III-2]. A case control study conducted within a large managed care organisation found that self reported exposures to vapours, gas, dust and fumes on the longest held job were responsible for 31% of COPD.(Blanc et al., 2009) Joint exposure both to smoking and occupational factors markedly increased the risk of COPD [evidence level III-2]. A summary of the risks of COPD associated with biological or mineral dusts, gases, fumes / vapours, diesel exhaust, irritant gases / vapours, chemical gas / fumes and various other occupational exposures appears in **Figure 3** (reproduced from Diaz-Guzman et al 2012(Diaz-Guzman et al., 2012) with permission).

**Figure 3: Risk of occupational exposure for COPD from selected studies**



Fortunately the air quality in most Australian and New Zealand cities is relatively good and cooking with biomass fuels (coal, wood, dung, crop waste etc) is uncommon. However a panel study of 84 moderate to severe COPD patients found that indoor pollutant exposure, including PM<sub>2.5</sub> and NO<sub>2</sub> (oxides of nitrogen) was associated with increased respiratory symptoms and risk of COPD exacerbation (Hansel et al., 2013) [evidence level III-2]. 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<sub>1</sub> compared with male smokers (Gan et al., 2006) [evidence level II]. On the other hand, a family based case control study involving high resolution chest CT scans found that men demonstrated more low attenuation areas consistent with emphysema than did women (Camp et al., 2009) [evidence level III-2]. 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. (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2006)

Novel risk factors for COPD have been reviewed by an assembly of the American Thoracic Society (Eisner et al., 2010a). Exposure to Secondhand (Environmental) Tobacco Smoke was consistently associated with various definitions of COPD; there was a temporal relationship, dose response gradient and biological plausibility. Meta-analysis of 12 studies found a pooled odds ratio of 1.56 (95%CI 1.40 - 1.74). There was sufficient evidence that exposure to smoke from burning biomass fuels was associated with development of COPD in women. Meta-analysis of 15 studies found a pooled odds ratio of 2.23 (95%CI 1.72 - 2.90), but there was significant heterogeneity between studies. [evidence level III-2]. Whilst the risk of biomass smoke in men has only been assessed in three studies, there also appears to be a similarly increased risk of COPD (OR 4.3, 95%CI 1.85-10) (Hu et al., 2010). Pulmonary tuberculosis can lead to scarring and irreversible loss of lung function, however there is currently insufficient evidence that this is clinically similar to COPD caused by cigarette smoking (Eisner et al., 2010a).

## Box 2: Risk Factors for COPD (Global Initiative for Chronic Obstructive Lung Disease, 2009)

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

Previous tuberculosis

Socioeconomic status

Nutrition

Comorbidities

### C1.1 Natural history

Although FEV<sub>1</sub> has long been accepted as the single best predictor of mortality in population studies in COPD (Fletcher and Peto, 1977), (Peto et al., 1983) 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. (Casanova et al., 2005) Exercise capacity (as measured by the 6 minute walk distance (6MWD), incremental shuttle walk distance (ISWD), or peak VO<sub>2</sub> during a cardiopulmonary exercise 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<sub>1</sub> in patients with established disease. Several of these latter indices are incorporated together in a single score, the BODE index (Body mass index, degree of Obstruction as measured by FEV<sub>1</sub>, Dyspnoea score and Exercise capacity measured by 6MWD) or the i-BODE index, in which the ISWD replaces the 6MWD strongly predicts mortality. (Celli et al., 2004), (Williams et al., 2012) A simplified ADO index (Age, Dyspnoea score and Obstruction) has been developed in a Swiss cohort and shown to predict three year mortality in a Spanish cohort (Puhan et al., 2009b) [evidence level III-2]. Further studies are awaited including validation in an Australian cohort of COPD patients. Nonetheless, FEV<sub>1</sub> 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<sub>1</sub> <20% predicted, 30% for those with FEV<sub>1</sub> of 20%–29% predicted and about 50% for those with an FEV<sub>1</sub> of 30%–39% predicted. (Connors et al., 1996) Patients with an FEV<sub>1</sub> <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. (National Emphysema Treatment Trial Research, 2001) A review of 15 COPD prognostic indices found that although the prognostic information of some has been validated, they lack evidence for implementation. Impact studies will be required in the future to determine whether such indices improve COPD management and patient outcomes. (Dijk et al., 2011)

Continued smoking and airway hyperresponsiveness are associated with accelerated loss of lung function. (Tashkin et al., 1996) 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 (Tashkin et al., 1996), (Anthonisen et al., 2002)

The development of hypoxaemic respiratory failure is an independent predictor of mortality, with a three-year survival of about 40%. (Medical Research Council Working Party, 1981) Long term administration of oxygen increases survival to about 50% with nocturnal oxygen (Medical Research Council Working Party, 1981) and to about 60% with oxygen administration for more than 15 hours a day (Nocturnal Oxygen Therapy Trial Group, 1980) (see also section P). There may be a differential in benefit between men and women. A study (Ekstrom et al.) of Swedish patients receiving long term oxygen therapy demonstrated that overall, women had a lower risk of death than men; nonetheless, when compared with expected death rates for the population, women had a higher relative mortality with a standardised mortality rate (SMR) of 12 (95% CI; 11.6-12.5) compared with 7.4 (95% CI 7.1-7.6) [evidence level III-2].

The natural history of COPD is characterised by progressive deterioration with episodes of acute deterioration in symptoms referred to as acute exacerbations. A large study that included 4951 patients from 28 countries found that health-related quality of life, measured by the SGRQ, deteriorated faster in patients with more severe disease (Jones et al., 2011a). Patients then classified as in GOLD stage II who received placebo showed an overall improvement, while those in GOLD stages III and IV deteriorated. When all participants from the different arms were included, the change in SGRQ at three years correlated weakly with change in

FEV<sub>1</sub>:  $r = -0.24$ ,  $p < 0.0001$  and there was no difference in this relationship between men and women. However, a significantly faster deterioration in the SGRQ score relative to FEV<sub>1</sub> % predicted was seen in older patients (greater 65 years).

Admission to hospital with an acute 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<sub>2</sub>) >50mmHg.(Connors et al., 1996) For those with chronic carbon dioxide retention (about 25% of those admitted with hypercapnic exacerbations), the five-year survival was only 11%.(Connors et al., 1996)

## C2. Diagnosis

### C2.1 History

Consider COPD in all smokers and ex-smokers over the age of 35 years(Fletcher and Peto, 1977) [evidence level II]

The main symptoms of COPD are breathlessness, cough and sputum production. 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.(Thompson et al., 1992) People with chronic cough and sputum are at increased risk of exacerbation (Burgel et al., 2009) [evidence level III-2]. 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 effect of breathlessness on daily activities can be quantified easily in clinical practice using the Modified Medical Research Council (mMRC) Dyspnoea Scale (see **Box 3**) (Celli et al., 2004, Fletcher et al., 1960).

#### **Box 3: Modified Medical Research Council (mMRC) Dyspnoea Scale for grading the severity of breathlessness during daily activities**

Grade	Description of Breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 metres or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing or undressing

The COPD assessment test (CAT)(Jones et al., 2009) may provide useful information when taking a history from patients. The CAT quantifies the impact COPD has on a patient's wellbeing and daily life, with the aim of facilitating communication between healthcare professionals and patients. The test is comprised of eight questions pertaining to cough, sputum, chest tightness, exercise tolerance, ability to perform activities of daily living, confidence in leaving the home, sleep and energy levels. The CAT is freely available in many languages (see <http://www.catestonline.org/english/index.htm>). It is easy and quick to complete, and score.

### C2.2 Physical examination

The sensitivity of physical examination for detecting mild to moderate COPD is poor.(Badgett et al., 1993) 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.(Badgett et al., 1993) 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 is dominated by large airway resistance and has a wide range of normal values. (Kelly and Gibson, 1988)

### C2.3 Spirometry

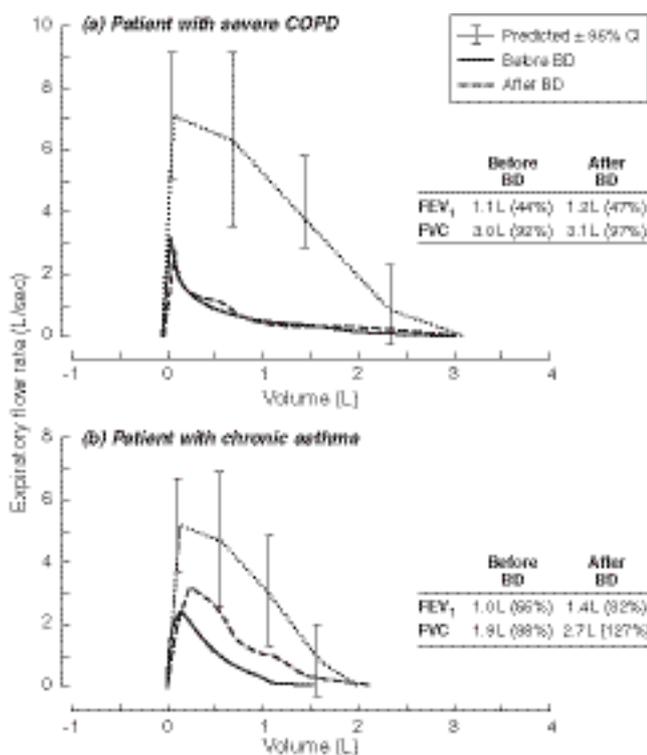
The diagnosis of COPD rests on the demonstration of airflow limitation which is not fully reversible (NHLBI/WHO Workshop Report, April 2001) [evidence level II]

It is important in general practice settings to obtain accurate spirometric assessment (Walters et al., 2011b) [evidence level III-3]

Because COPD is defined by a post-bronchodilator FEV<sub>1</sub>/FVC ratio < 0.7, spirometry is essential for its diagnosis (see Figure 4) and this may be performed in the community or prior to discharge from hospital. (Rea et al., 2011) 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<sub>1</sub> to forced vital capacity (FVC) is <70% and the FEV<sub>1</sub> is <80% of the predicted value. The ratio of FEV<sub>1</sub> to vital capacity (VC) is a sensitive indicator for mild COPD. FEV<sub>1</sub>/FEV<sub>6</sub> has a high level of agreement with FEV<sub>1</sub>/FVC on both the fixed ratio and Lower Limit of Normal (LLN) criteria for the diagnosis of COPD. (Bhatt et al., 2014)

**Figure 4: 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<sub>1</sub>) was within the normal range (82% predicted). Absolute and per cent predicted values for FEV<sub>1</sub> 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 (Wilt et al., 2005) [evidence level I]. The current inaccuracy of diagnosis in community settings and the importance of using spirometry was demonstrated by an Australian study where only 58% of general practice patients being treated for COPD were confirmed to have the diagnosis on post-bronchodilator spirometry (Zwar et al., 2011). The unreliability of clinical assessment for the diagnosis of COPD has also been shown in a study in Dutch primary care. (Lucas et al., 2012) 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. (Miller et al., 2005)

#### **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.

There is evidence that in a general practice setting, patients with comorbidities may be more commonly mis-diagnosed with COPD. Spirometric assessment is important in these patients to minimise this risk. (Zwar et al., 2011)

### **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<sub>1</sub> is within the normal range (>80%).

### **C2.5 COPD screening devices for targeted case finding**

COPD screening devices are simple lung function tools to assist practitioners in the screening of individuals who are at risk of COPD. The devices measure the amount of exhaled air in the first 1 and 6 seconds of expiration (FEV<sub>1</sub>, FEV<sub>6</sub>) and calculate FEV<sub>1</sub>/FEV<sub>6</sub>, which is the ratio of the amount of air forcibly exhaled in the first second relative to the first 6 seconds. Lung Foundation Australia's *Position Paper on the Use of COPD screening devices for targeted COPD case finding in community settings*, <http://lungfoundation.com.au/wp-content/uploads/2014/02/Position-Paper.pdf> recommends that previously undiagnosed individuals aged 35 years or older should be screened with the screening symptom checklist, followed by a COPD screening device with an FEV<sub>1</sub>/FEV<sub>6</sub> cut-off < 0.75. Symptomatic or at-risk individuals with an FEV<sub>1</sub>/FEV<sub>6</sub> ratio < 0.75 should undergo formal diagnostic spirometry. Symptomatic or at-risk individuals with an FEV<sub>1</sub>/FEV<sub>6</sub> ratio ≥ 0.75 should be encouraged to visit their general practitioner as they may be at risk of other diseases or lung conditions and may require more formalised testing.<sup>†</sup>

## **C3. Assessing the severity of COPD**

Spirometry is the most reproducible, standardised and objective way of measuring airflow limitation, and FEV<sub>1</sub> is the variable most closely associated with prognosis. (Peto et al., 1983) The grades of severity according to FEV<sub>1</sub> and the likely symptoms and complications are shown in **Box 4**. However, it should be noted that some patients with an FEV<sub>1</sub> >80% predicted, although within the normal range, may have airflow limitation (FEV<sub>1</sub>/FVC ratio <70%).

A Spanish cohort study of 611 COPD patients found that the British Thoracic Society classification (which is very similar to Box 4) had the optimal sensitivity and specificity against the criterion of all cause and respiratory mortality over 5 years. (Esteban et al., 2009) There were also significant differences in health related quality of life between different stages of the disease [evidence level III-2].

Exacerbations are an important complication of COPD (see X: Manage eXacerbations). The future risk of exacerbations should be assessed in patients with COPD ((GOLD), 2014). Exacerbations are more frequent with increased severity of COPD. The most important risk factor for exacerbations is a history of past exacerbations; other factors include gastro-oesophageal reflux, poorer quality of life and elevated white cell count (Hurst et al., 2010).

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<sup>†</sup> Level of evidence could not be assigned due to heterogeneity

**Box 4: Classification of severity of chronic obstructive pulmonary disease (COPD)**

	MILD	MODERATE	SEVERE
<b>Typical Symptoms</b>	Few symptoms	Increasing dyspnoea	Dyspnoea on minimal exertion
	Breathlessness on moderate exertion	Breathlessness walking on level ground	Daily activities severely curtailed
	Recurrent chest infections	Increasing limitation of daily activities	Experiencing regular sputum production
	Little or no effect on daily activities	Cough and sputum production	Chronic cough
		Infections requiring steroids	
<b>Lung Function</b>	FEV <sub>1</sub> ≈ 60-80% predicted	FEV <sub>1</sub> ≈ 40-59% predicted	FEV <sub>1</sub> < 40% predicted

FEV<sub>1</sub>=forced expiratory volume in one second

Box adapted from Lung Foundation Australia’s Stepwise Management of Stable COPD available at <http://lungfoundation.com.au/health-professionals/guidelines/stepwise-management-of-stable-copd/>

**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 asthma.

The details for this assessment are outlined in **Box 5**.

The change in FEV<sub>1</sub> 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 (e.g., 12% increase). An increase in FEV<sub>1</sub> of more than 12% and 200mL is greater than average day-to-day variability and is unlikely to occur by chance. (Sourk and Nugent, 1983), (Pellegrino et al., 2005) An analysis of cross-sectional data from 3,922 healthy never smokers in the BOLD study (Tan et al., 2012) found that the 95%les (95% CI) for bronchodilator response were 284 ml (263 to 305) absolute change in forced expiratory volume in 1 second from baseline. However, this degree of reversibility is not diagnostic of asthma and is frequently seen in patients with COPD (e.g., the FEV<sub>1</sub> 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 5: 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<sub>1</sub> <80% predicted and FEV<sub>1</sub>/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 (e.g., 200–400mcg salbutamol from MDI and spacer).

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

FEV<sub>1</sub>=forced expiratory flow in one second.

FVC=forced vital capacity.

### C4.1 Confirm or exclude asthma

If airflow limitation is fully or substantially reversible, (FEV<sub>1</sub> response to bronchodilator >400ml), the patient should be treated as for asthma (British Thoracic Society, 2008a), (Hunter et al., 2002)

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 (e.g., 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 may be considered are shown in **Box 6**.

#### Box 6: 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 <sub>1</sub>	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<sub>1</sub>, forced expiratory volume in 1s; COPD, chronic obstructive pulmonary disease.

Box adapted from British Thoracic Society Statement (British Thoracic Society, 2008b)

#### C5.1 Complex lung function tests

Other measurements of lung function such as static lung volumes and diffusing capacity of lungs for carbon monoxide assist in the assessment of patients with more complex respiratory disorders. Measurements such as inspiratory capacity (IC), which indicate the degree of hyperinflation and relate to exercise tolerance (O'Donnell et al., 2001) and mortality (Casanova et al., 2005) and forced oscillometry, have not yet found clinical application.

## **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 (e.g., 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.

## **C5.3 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 for the diagnosis of COPD as hyperinflation is not specific 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 (e.g., 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 (e.g., whose FEV<sub>1</sub> is <40% predicted or <1L, whose oxygen saturation as measured by pulse oximetry [SpO<sub>2</sub>] is <92%), those with pulmonary hypertension, and those with breathlessness out of proportion to their clinical status). Respiratory failure is defined as a PaO<sub>2</sub><60mmHg (8kPa) or PaCO<sub>2</sub>>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) alpha<sub>1</sub> antitrypsin deficiency has been estimated at between 1/4,348 and 1/5,139 in European populations (Blanco et al., 2006). Available data from 15 cohorts in Australia and New Zealand suggest that the prevalence of affected individuals is around 1/4000. (de Serres, 2002) 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 alpha<sub>1</sub> AT deficiency (American Thoracic Society/European Respiratory Society, 2003). 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 alpha<sub>1</sub> antitrypsin and if reduced, genotyping should be performed.

### C5.11 Electrocardiography and echocardiography

Cardiovascular disease is common in patients with chronic obstructive pulmonary disease but is often under-recognised. Electrocardiography (ECG) may be useful to alert the clinician to its presence. In a retrospective Dutch study of patients entering pulmonary rehabilitation, ischaemic changes were present on ECG in 21% of all patients and in 14% of those without reported cardiovascular co-morbidity. (Vanfleteren et al., 2011) Electrocardiography is also indicated to confirm arrhythmias 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. (McCord and Borzak, 1998) 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 (National Heart Lung and Blood Institute, 1998), (Decramer et al., 2005), (Holguin et al., 2005) [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. (National Heart Lung and Blood Institute, 1998) 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. (Borrill et al., 2003) 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. Adherence to inhaled medications regimes is associated with reduced risk of death and admissions to hospital due to exacerbations in COPD (Vestbo et al., 2009) [evidence level II].

### **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. Optimal management of any individual patient with COPD must include careful management of comorbidities and anticipation of increased risks associated with those comorbidities in the presence of COPD.
- **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<sup>‡</sup> 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.

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<sup>‡</sup> 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 (Vathenen et al., 1988, Gross et al., 1989, Higgins et al., 1991, Belman et al., 1996, Jenkins et al., 1987, Guyatt et al., 1987, Berger and Smith, 1988, Hay et al., 1992) [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 (Ram and Sestini, 2003) found a significant increase in post-bronchodilator spirometry when compared to placebo; weighted mean difference = 140mls (95% CI 40 to 250) for FEV<sub>1</sub> 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 (Guyatt et al., 1987). 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 (antimuscarinics)

The duration of action of short-acting anticholinergics (antimuscarinics) 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 (Appleton et al., 2006a). Ipratropium bromide improved spirometry over short-acting beta-agonists alone, weighted mean difference = 30mls (95% CI 0 to 60) for FEV<sub>1</sub> 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 minor 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 corticosteroids for participants receiving ipratropium bromide, with 15 (95% CI 12 – 28) people requiring treatment with ipratropium bromide to prevent one receiving additional oral corticosteroids.

However, some studies have found that ipratropium bromide is associated with an increased risk of adverse cardiovascular effects (Lee et al., 2008, Singh et al., 2008, Ogale et al., 2010). A nested case-control study (Lee et al., 2008) [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 (Singh et al., 2008) 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].

A Cochrane meta-analysis comparing treatment with tiotropium [HandiHaler or Respimat] with ipratropium bromide (via MDI) for patients with stable COPD found that tiotropium treatment, was associated with improved lung function, fewer hospital admissions (including those for exacerbations of COPD), fewer exacerbations of COPD and improved quality of life. There were both fewer serious adverse events and disease specific events in the tiotropium group, but no significant difference in deaths with ipratropium bromide when compared to tiotropium. Thus, tiotropium appears to be a reasonable choice (instead of ipratropium bromide) for patients with stable COPD ((Cheyne et al., 2013))

#### 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 (Appleton et al., 2006a). 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<sub>1</sub> 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 corticosteroids 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 corticosteroid 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.

## O1.2 Long-acting bronchodilators

Long-acting bronchodilators produce significant improvements in lung function, symptoms and quality of life (Braidó et al., 2013), 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 (antimuscarinics)

Long-acting anticholinergic (antimuscarinic) agents e.g. tiotropium and glycopyrronium bromide cause bronchodilation with a duration of action of over 24 hours and are used once daily. (Maltais et al., 2011) Acclidinium bromide is another long-acting anticholinergic (antimuscarinic) used twice daily. (Karabis et al., 2013) A systematic review (Karner et al., 2012) found that tiotropium improved mean quality of life, increased the number of patients with a clinically significant improvement, and reduced the number of patients with a clinically significant deterioration in quality of life [evidence level I]. Tiotropium reduced the number of patients with an exacerbation (OR 0.78; 95% CI 0.70 to 0.87), corresponding to a number needed to treat (NNT) of 16 patients (95% CI 10 to 36) with tiotropium for a year in order to avoid one additional patient suffering exacerbations. Lung function improved with tiotropium, compared to placebo (trough FEV<sub>1</sub> mean difference 119 mL; 95% CI 113 to 125). There was no statistically significant difference in all-cause mortality between the tiotropium and placebo groups. (Wise et al., 2013). Systematic reviews (Barr et al., 2006), (Barr et al., 2005) found tiotropium produced a significant increase in FEV<sub>1</sub> of the order of 130mls compared to placebo. A 2011 meta-analysis (Yohannes et al., 2011) comparing tiotropium with placebo, ipratropium and the long-acting beta-agonist, salmeterol, included a larger number of patients (16,301) and found superior efficacy for quality of life, dyspnoea and exacerbation rates compared with placebo and ipratropium. The number of patients needed to treat with tiotropium was 22 (95% CI 13 to 65) to prevent one exacerbation compared to placebo. No significant differences between tiotropium and salmeterol were found for any outcome. Dry mouth was the most common adverse event reported and the proportion of patients experiencing a dry mouth was higher in those using tiotropium than any of placebo, ipratropium or salmeterol (NNH compared to placebo = 25, 95%CI 12 to 66). Pneumonia rates were not analysed.

Many of these effects have been confirmed in a large four-year randomised-controlled trial, whose primary outcome was the effect of tiotropium on the rate of decline in lung function. (Tashkin et al., 2008) Tiotropium produced no effect on the rate of decline of FEV<sub>1</sub> or FVC, but both measurements were significantly higher in the tiotropium group when compared to placebo at all time points following randomisation (mean pre-bronchodilator difference in FEV<sub>1</sub> = 87 to 103 mls). Tiotropium was associated with improved HRQL at all time points (mean difference in total SGRQ for all time points = 2.7, 95% CI 2.0 to 3.3) and a delay to time of first exacerbation (tiotropium = 16.7 months vs. placebo = 12.5 months).

In an international, multi-centre, double blind placebo controlled trial, Vogelmeier et al randomised 7,376 patients with moderate to severe COPD and a history of exacerbations to either salmeterol or tiotropium. (Vogelmeier et al., 2011) Tiotropium increased the time to first exacerbation by 42 days compared to salmeterol (187 vs. 145 days) corresponding to a reduction in risk by 17% (hazard ratio 0.83; 95% CI 0.77 to 0.90) [evidence level II].

The beneficial effects come at a cost of increased adverse drug effects. A pooled study of placebo controlled trials (Kesten et al., 2006) 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 9.5). A population based nested case control study of COPD patients found that if 514 (95% CI 336-905) men with benign prostatic hypertrophy were commenced on inhaled antimuscarinics, one would develop acute urinary retention (Stephenson et al., 2011) [evidence level III-2]. These effects have been confirmed in a large four-year randomised-controlled trial (Tashkin et al., 2008) 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. However, it is important to note that patients with unstable arrhythmias, a history of heart failure or heart attack within the previous 6 months were excluded from this trial. (Singh et al., 2013)

Direct comparison and mixed treatment comparison (MTC) meta-analyses of 42 randomised controlled, double-blind trials lasting 6 months or more were conducted in patients receiving tiotropium Soft Mist Inhaler, tiotropium Handihaler, long-acting beta2 agonist (LABA), inhaled corticosteroid (ICS) and LABA-ICS combination. (Dong et al., 2013) A total of 52, 516 patients with COPD (64 years of age, 73% men, 37% current smokers, and 44% of predicted value in FEV<sub>1</sub>) were enrolled in these trials which assessed overall death (primary outcome) and cardiovascular death (secondary outcome). Patients using tiotropium Soft Mist Inhaler had universally increased risks compared with those receiving placebo (OR 1.51; 95% CrI 1.06 to 2.19) or those using tiotropium HandiHaler (OR 1.65; 95% CrI 1.13 to 2.43), LABA (OR 1.63; 95% CrI 1.10 to 2.44) and LABA-ICS (OR

1.90; 95% CrI 1.28 to 2.86). In contrast, LABA-ICS demonstrated a beneficial profile versus placebo (OR 0.80; 95% CrI 0.67 to 0.94) or ICS (OR 0.77; 95% CrI 0.64 to 0.93). For cardiovascular death, tiotropium Soft Mist Inhaler had a more apparent risk compared with placebo (OR 2.07; 95% CrI 1.09 to 4.16), tiotropium HandiHaler (OR 2.38; 95% CrI 1.20 to 4.99), LABA (OR 3.04; 95% CrI 1.48 to 6.55), LABA-ICS (OR 2.79; 95% CrI 1.37 to 6.02) and ICS (OR 2.39; 95% CrI 1.18 to 5.12). In contrast, LABA had a decreased risk versus placebo (OR 0.68; 95% CrI 0.50 to 0.93).

Tiotropium Soft Mist Inhaler consistently demonstrated an increased risk of overall death versus any comparators, and showed an increased risk of cardiovascular death versus LABA-ICS. The analyses restricted to trials with longer treatment duration and trials enrolling patients with severe COPD showed similar results to the main analysis, although the risk of cardiovascular death associated with tiotropium Soft Mist Inhaler was slightly higher for patients with severe COPD. Use of 10 µg/day tiotropium Soft Mist Inhaler tended to be associated with a higher risk of overall death against all comparators, although the risks of cardiovascular death were irrespective of the dose of tiotropium. A prospective study (Wise et al., 2013) has allayed concerns re.g.arding use of lower doses of tiotropium delivered by Soft Mist Respimat Inhaler and the risk of death in COPD. In a large prospective double blind parallel group RCT of tiotropium delivered via Respimat Misthaler 2.5 or 5µg or via Handihaler 18µg there was no increased risk of death in either of the two Respimat arms compared with the Handihaler arm [HR for Respimat 5 µg v Handihaler was 0.96 (95% CI 0.84-1.09); for Respimat 2.5µg v Handihaler HR 1.00(95% CI 0.87-1.14)]. The study included patients with concomitant heart disease but excluded patients with myocardial infarction in the previous six months or who had been hospitalised for Class 3 or 4 heart failure or had had an unstable or life-threatening arrhythmia requiring new treatment within the previous 12 months. Also excluded were patients with moderate or severe renal impairment. Death from any cause in the groups was just over 7% in each arm and cardiovascular death just on 2% in each. Rates of exacerbation were similar in all three groups. This study suggests that tiotropium delivered in doses no higher than 5µg via the Soft Mist Respimat Inhaler device appears to be as safe and efficacious as that delivered via Handihaler, but prescribers should be aware of the exclusion criteria for such trials and use caution in patients with characteristics which would have excluded them from this trial. Until more evidence is available, the use of tiotropium Soft Mist Inhaler should be with caution and the dose should not exceed the recommended daily dose (5µg).

Glycopyrronium bromide (NVA237) is another inhaled, once daily, long-acting anti-muscarinic agent. In a non-inferiority, double blind randomised, controlled clinical trial, Chapman et al compared glycopyrronium to tiotropium.(Chapman et al., 2014) The trial was only 12 weeks in duration. No difference was found with respect to trough FEV<sub>1</sub>, dyspnoea, quality of life, exacerbations or side effects. Two randomised controlled trials have demonstrated significant improvement in spirometry and a reduction in moderate to severe exacerbations compared with placebo; there was no difference in quality of life(D'Urzo et al., 2011, Kerwin et al., 2012). One of these trials also randomised patients to tiotropium and found that glycopyrronium was not inferior with re.g.ards to spirometry, quality of life and moderate to severe exacerbations(Kerwin et al., 2012) [evidence level II].

Aclidinium is a long-acting antimuscarinic agent used twice daily. Two randomised controlled trials of 12 to 24 weeks duration have demonstrated improved bronchodilation (trough and peak FEV<sub>1</sub>), quality of life (SGRQ) and dyspnoea (TDI) with aclidinium, compared with placebo(Kerwin et al., 2012, Jones et al., 2012) [evidence level II].

### O1.2.2 Long-acting beta-agonists

Long-acting beta-agonists cause prolonged bronchodilatation and can be administered once (indacaterol) or twice daily (salmeterol, formoterol). A systematic review of randomised controlled trials(Appleton et al., 2006b) 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.

Treatment using salmeterol 50µg twice daily or formoterol 12µg twice daily has been found to be associated with improved patient quality of life (Kew et al., 2013). LABA treatment has been shown to reduce exacerbations, including those requiring hospitalisation, but the evidence is of moderate quality and confounded by concomitant ICS use. LABAs did not significantly reduce mortality or serious adverse events.

Indacaterol is an inhaled ultra long-acting beta<sub>2</sub> agonist that can be given as a once daily maintenance therapy for COPD. Compared to placebo, indacaterol improves dyspnoea(Han et al., 2013, Jiang et al., 2013) [evidence level I], FEV<sub>1</sub> and health-related quality of life, and reduces exacerbations(Dahl et al., 2010), (Donohue et al., 2010), (Chapman et al., 2011), (Jones et al., 2011b), (Kornmann et al., 2011)[evidence level II]. The bronchodilator effects of indacaterol are at least as good as tiotropium(Donohue et al., 2010), formoterol (Dahl et al., 2010) or salmeterol. (Kornmann et al., 2011) (Cope et al., 2013) although long term effects beyond 52 weeks have not been studied. (Jiang 2013)

The efficacy of long-acting beta-agonists compared to ipratropium bromide alone, or in combination, have also been combined in a systematic review.(Appleton et al., 2006a) Comparisons of monotherapy found a greater increase in FEV<sub>1</sub>, 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).

### 01.2.3 Long-acting bronchodilator combinations

A Cochrane systematic review of five studies found that the combination of tiotropium and a long-acting beta-agonist provided small improvements in health-related quality of life (mean difference in total SGRQ of -1.61, 95% CI -2.93 to -0.29 over 6 to 12 months) and bronchodilation (mean difference in pre-bronchodilator FEV<sub>1</sub> 0.07 L; 95% CI 0.05 to 0.09), compared to tiotropium alone (Kärner and Cates, 2012) [evidence level I]. It should be noted that the majority of participants in these studies had severe COPD. The clinical importance of these small benefits was uncertain. No statistically significant differences in mortality or hospital admissions were found.

Dual bronchodilation with a combination of indacaterol and glycopyrronium, given once daily, was found to increase FEV<sub>1</sub> (pre-dose) compared to the monocomponents, tiotropium (Bateman et al., 2013) (with a comparable safety profile (Dahl et al., 2013)) or placebo (Bateman et al., 2013, Dahl et al., 2013, Wedzicha et al., 2013) [evidence level II]. Moderate to severe exacerbations were reduced by 12% with the combination compared to glycopyrronium (Wedzicha et al., 2013). The combination of indacaterol and glycopyrronium showed favourable improvements in lung function over salmeterol-fluticasone in a study of moderate to severe COPD patients without exacerbations in the previous year (Vogelmeier et al., 2013) [evidence level II].

### 01.3 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<sub>1</sub>. Other objective measurements, such as an increase in exercise capacity (e.g., as measured using a walking test such as the six minute walk test or the incremental or endurance shuttle walking test (Pepin et al., 2007, Pepin et al., 2005) 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).

## 02. Oral bronchodilators

### 02.1 Methylxanthines

Theophylline has a modest effect on FEV<sub>1</sub> and FVC (Molfinio and Zhang, 2006) 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 adverse effects. (Chrystyn et al., 1988), (Ram et al., 2002) Some patients with disabling breathlessness may, however, derive benefit from their use. (Murciano et al., 1989, McKay et al., 1993, Taylor et al., 1985) Therapeutic drug monitoring of theophylline is recommended to reduce the risk of toxicity and to distinguish non adherence, under-treatment and therapeutic failure. Theophyllines may have an anti-inflammatory effect or reduce muscle fatigue. (Aubier, 1988), (Moxham, 1988) Studies have suggested lower dose preparations than had previously been used (achieving plasma concentrations of 5-10mg/L) may have anti-inflammatory or immuno-modulatory effects. (Barnes, 2003, Kobayashi et al., 2004, Cosio et al., 2009) A randomised placebo controlled trial in China demonstrated that doses of 100mg twice daily reduced exacerbations compared with placebo. (Zhou et al., 2006) Evidence supports only the slow-release formulation. Theophylline has some efficacy 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 (MIMS Australia Pty Ltd, 2008)), inhaled bronchodilators are preferred when available. (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2006) Theophylline has an extensive drug interaction profile that may present potential adverse effects in patients on some multi-medication regimens. If medications are started or stopped, pharmacokinetic interactions can be detected by changes in theophylline concentrations. For example, erythromycin and clarithromycin inhibit theophylline metabolism with

consequent increase in plasma theophylline concentration and decrease in plasma theophylline concentration on stopping.

## O2.2 Phosphodiesterase type-4 inhibitors

Cilomilast and roflumilast which are not currently available in Australia are inhibitors of phosphodiesterase type-4 (PDE-4). They act by increasing intracellular concentrations of cyclic adenosine monophosphate and causing a range of anti-inflammatory effects. Placebo controlled studies of up to six months duration (Rennard et al., 2006), (Rabe et al., 2005) 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<sub>1</sub>, by an order of 40 - 100ml, compared to placebo. Placebo controlled RCTs have now been extended to 52 weeks. (Calverley et al., 2009) They confirm a consistent improvement in pre-bronchodilator FEV<sub>1</sub> and a 17% reduction in the annual rate of exacerbations with roflumilast. The effects on lung function, exacerbations and breathlessness are additive to those of long acting bronchodilators such as salmeterol and tiotropium (Fabbri et al., 2009) [evidence level II]. A Cochrane meta-analysis (Chong et al., 2013) concluded that although PDE4 inhibitors improve short term lung function and reduce exacerbations (OR 0.78 95% CI 0.72-0.85), they lead, overall, to marginal improvements in health related quality of life and symptoms.

Drug related adverse effects mainly affect the gastrointestinal system; diarrhoea, abdominal pain, nausea and vomiting and weight loss are 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 corticosteroids.

## O3. Corticosteroids

Long term use of systemic corticosteroids is not recommended (Postma et al., 1988, Postma et al., 1985, Decramer et al., 1996, Decramer et al., 1994, Decramer and Stas, 1992) [evidence level I]

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

### O3.1 Oral corticosteroids

Some patients with stable COPD show a significant response to oral corticosteroids (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 corticosteroids (<14 days) do not require tapering. A negative bronchodilator response does not predict a negative steroid response. (NHLBI/WHO Workshop Report, April 2001), (Senderovitz et al., 1999) If there is a response to oral steroids, continued treatment with inhaled corticosteroids is indicated, but these may fail to maintain the response. (Senderovitz et al., 1999), (Vestbo et al., 1999)

### O3.2 Inhaled corticosteroids

Inhaled corticosteroids should be considered in patients with moderate to severe COPD and frequent exacerbations [evidence level I]

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. (Miravittles et al., 2004) A number of randomised controlled trials of inhaled corticosteroids have been published and these have been combined in a systematic review (Yang et al., 2012) [evidence level I], mainly involving subjects without bronchodilator reversibility or bronchial hyper-responsiveness.

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

Inhaled corticosteroids alone do not improve mortality, with pooled results from nine studies involving 8,390 participants showing an odds ratio of death of 0.98 (95% CI 0.83 to 1.16). The effect of inhaled corticosteroids on the rate of decline in lung function is inconsistent. Pooled results from studies of six months duration or longer, show either no significant difference in the rate of decline in post-bronchodilator FEV<sub>1</sub> (generic inverse variance analysis: weighted mean difference of 5.8mls/year (95% CI -0.28 to 11.88, 2,333 participants) or a small statistically significant difference (pooled means analysis: 6.88 ml/year, 95% CI 1.80 to 11.96, 4823 participants, with the inclusion of the TORCH study. (Calverley et al., 2007, Yang et al., 2012)

Any potential benefits of inhaled corticosteroids should be weighed against the potential risks of local oropharyngeal adverse effects and pneumonia. Local adverse effects include increased risk of oral candidiasis (OR 2.65, 95% CI 2.03 to 3.46, 5586 participants) and hoarseness or dysphonia (OR 1.95, 95% CI 1.41 to 2.70, 3267 participants). (Yang et al., 2012) A meta-analysis of 43 COPD studies (26 fluticasone studies, n = 21,247; 17 budesonide studies, n = 10,150) has demonstrated an increased risk of pneumonia with use of inhaled corticosteroids, when given as monocomponents or in combination inhalers (Kew and Seniukovich, 2014). Non-fatal serious adverse pneumonia events (i.e. requiring hospital admission) were increased with fluticasone (OR 1.78, 95%CI 1.50 to 2.12) and budesonide (OR 1.62, 95% CI 1.00 to 2.62). There were no significant differences in serious adverse events or mortality when budesonide and fluticasone were compared indirectly. The risk of any pneumonia event was found to be higher with fluticasone than budesonide (OR 1.86, 95%CI 1.04 to 3.34), but this should be interpreted with caution due to differences in definitions of pneumonia in the trials. The authors recommended that safety concerns regarding increased pneumonia should be balanced against the benefits of reduced exacerbations and improved quality of life (Kew and Seniukovich, 2014).

In people with COPD and diabetes mellitus, particular care should be taken not to exceed the recommended dose of corticosteroids as there is some evidence of a direct relationship between corticosteroid dose and glucose levels in such patients (Slatore et al., 2009) [evidence level III-2].

Withdrawal of inhaled corticosteroids was not associated with any statistically significant increase in exacerbation rate in a systematic review of 4 RCTs in 901 patients (Nadeem et al., 2011) (OR 1.11, 95% CI 0.84 to 1.46) [evidence level I]. As there was much heterogeneity in definition of exacerbations in these RCTs and some outcomes (earlier exacerbations upon withdrawal of inhaled corticosteroids), there was insufficient evidence in the systematic review to recommend discontinuation of inhaled corticosteroids.

### **O3.3 Inhaled corticosteroids versus long-acting beta-agonists**

A systematic review of inhaled corticosteroids vs. long-acting beta-agonists in COPD found similar benefits in exacerbation rates and mortality when comparing these treatments, but there was a higher rate of pneumonia with inhaled corticosteroids (Spencer et al., 2011) [evidence level I]. There were small benefits in FEV<sub>1</sub> (for long-acting beta-agonists) and quality of life (for inhaled corticosteroids). Overall, the authors conclusions supported long-acting beta-agonists as part of frontline therapy for COPD, with regular inhaled corticosteroid therapy as an adjunct in patients experiencing frequent exacerbations (Spencer et al., 2011).

## **O4. Inhaled combination therapy**

### **O4.1 Inhaled corticosteroids and long-acting beta-agonists in combination**

A systematic review of 19 randomised controlled trials involving 10,400 COPD patients of combined corticosteroids and long-acting beta<sub>2</sub>-agonists in one inhaler (Nannini et al., 2013a) [evidence level I] found that, compared with placebo, both fluticasone/salmeterol and budesonide/formoterol reduced the rate of exacerbations (rate ratio 0.73; 95% CI 0.69 to 0.78). It was estimated that treatment with combined therapy would lead to a reduction of one exacerbation every two to four years. The three-year number needed to treat for an additional beneficial outcome (NNTB) with fluticasone/salmeterol to prevent one extra death was estimated at 42 (95% CI 24 to 775). Combined treatments improved health status to a small extent and improved lung function. Increased risk of pneumonia was observed with combined treatments compared with placebo (OR 1.62, 95% CI 1.36 to 1.94), with a three-year NNTB for one additional case of pneumonia estimated to be 17. However, exacerbations, hospitalisations or deaths did not increase. Overall, the authors concluded that there were no major differences between combined inhalers in terms of benefits, but the evidence was currently not strong enough to demonstrate that all are equivalent. Data from Kliber (Kliber et al., 2010) [evidence level I] in 30,495 patients with COPD enrolled in trials of six months or greater duration found combination therapy, compared with placebo, was associated with a reduction in all-cause mortality, relative risk 0.80 (95% CI 0.69, 0.94).

Studies have found conflicting results when the different combination therapies were compared with the mono-components alone. A systematic review by Nannini et al (Nannini et al., 2012) of 14 studies (11,784 participants) found low quality evidence for reduced exacerbation rates (rate ratio 0.76; 95% CI 0.68 to 0.84) with ICS/LABA vs. LABA alone [evidence level I]. There was no statistically significant difference in hospitalisations or mortality. ICS/LABA improved quality of life and FEV<sub>1</sub> to a small extent, compared to LABA alone. High attrition rates from the studies limited the confidence in the results, except the mortality result. Pneumonia was observed more commonly with ICS/LABA use (OR 1.55; 95% CI 1.20 to 2.01) with an annual risk of 4% on combination treatment, compared to 3% on LABA alone. In 2012, Sharafkaneh et al reported that budesonide/formoterol 320/9 mg compared with formoterol alone prolonged the mean time to first exacerbation (277.9 days versus 249.8 days; p= 0.029). Higher pneumonia rates were noted with budesonide/formoterol 320/9 mg 6.4% compared with 2.7% for formoterol alone. (Sharafkaneh et al., 2013)

A systematic review of 15 randomised controlled trials involving 7,814 COPD patients of combined corticosteroids and long-

acting beta2-agonists in one inhaler vs. inhaled steroids alone (Nannini et al., 2013b) [evidence level I] found that, compared with inhaled steroids, exacerbation rates were significantly reduced with combination therapies (rate ratio 0.87, 95% CI 0.80 to 0.94). Mortality was lower with combination therapy (odds ratio 0.78, 95% CI 0.64 to 0.94), mainly due to results from the TORCH study. There was a small improvement in lung function and health-related quality of life. The authors concluded that combination ICS/LABA inhalers offer some clinical benefits in COPD compared with ICS alone, especially for reduction in exacerbations. The review did not support the use of ICS alone when LABAs are available.

Compared to placebo, combination therapy did not significantly increase other adverse events, but oral candidiasis was significantly more common, (NNH 16 [8-36], 1436 participants). Combination therapy was not associated with more adverse effects compared to long-acting beta<sub>2</sub>-agonists. Chen et al (Chen et al., 2011) conducted a retrospective cohort study of Veterans Affairs (VA) patients with COPD who were admitted for pneumonia. Prior use of inhaled corticosteroids was associated with significantly reduced 30 and 90 day mortality and need for mechanical ventilation. The analysis adjusted for age, gender, race, marital status, primary care, classes of medications, smoking, comorbidities etc. However the patients were 98% male and the most common inhaled steroids were fluticasone and triamcinolone. [evidence level III-2]. Studies by Calverley (Calverley et al., 2007) and Kardos (Kardos et al., 2007) have found an increased rate of pneumonia (defined on clinical grounds) in the inhaled corticosteroid arms, and this was also found in the Rodrigo systematic review, NNH = 48 (95% CI 31, 85) (Rodrigo et al., 2009). These results contrast with the reductions in exacerbation rates induced by these drugs. A nested case control study from Canada (Ernst et al., 2007) [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 corticosteroids and that this appeared dose-related. In the two year RCT of salmeterol/fluticasone vs. tiotropium (Wedzicha et al., 2008), the number of *de novo* pneumonias not preceded by symptoms of exacerbations was similar between the two treatment groups. (Calverley et al., 2011) However, unresolved exacerbations preceding pneumonia were more common in the salmeterol/fluticasone-treated patients (32 exacerbations in 658 patients), compared to the tiotropium-treated group (7 exacerbations in 665 patients) [evidence level II]. 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. A network meta-analysis of 71 RCTs of 73,062 patients with COPD showed that quality of life and lung function improved most with combination ICS/LABA inhalers, with LABA or LAMA inhalers next in efficacy, and ICS alone least effective (Kew et al., 2014). Many of the patients in these studies had FEV<sub>1</sub> <50% predicted.

#### **O4.2 Inhaled corticosteroids and long-acting beta-agonists and long-acting anticholinergics (antimuscarinics) in combination**

More data is becoming available on the efficacy of multiple inhaled medications to guide the best combination that will optimise patient's lung function, improve symptoms and reduce exacerbations. A two-year double-blind, double dummy randomised controlled trial comparing tiotropium and combination therapy with fluticasone/salmeterol (500/50µg bd) (Wedzicha et al., 2008) found no difference in exacerbation rates between the groups (the primary aim of the study), but 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]. A systematic review incorporating this study concluded that the high and unbalanced withdrawal rate made interpretation of intervention effects difficult. (Welsh et al., 2013)

Studies of "triple therapy" with inhaled corticosteroids and long-acting beta-agonists and long-acting anticholinergics (antimuscarinics) in combination have revealed conflicting results. A Cochrane systematic review of "triple" therapy studies found uncertainty re.g.arding the long-term benefits and risks of treatment with tiotropium in addition to inhaled corticosteroid and long-acting beta<sub>2</sub>-agonist combination therapy on mortality, hospitalisation, exacerbations of COPD and pneumonia. (Karner and Cates, 2011) The systematic review found that the addition of combination treatment to tiotropium improves health-related quality of life and lung function [evidence level I]. A 12-week study of budesonide/formoterol with or without tiotropium (Welte et al., 2009) [evidence level II] found a significant increase in FEV<sub>1</sub>, the primary outcome, with triple therapy, mean difference pre-dosing 128 (95% CI 78, 179) mls. Similar effects on FEV<sub>1</sub> were found with the combination of tiotropium and salmeterol/fluticasone. (Hanania et al., 2012), (Jung et al., 2012)

There was a significant benefit in symptom control and also reduction in severe (systemic corticosteroids and/or hospitalisation/Emergency visit) exacerbations NNT = 9 (95% CI 8, 13). However, a longer term randomised double blind placebo-controlled study of one year comparing salmeterol or combined salmeterol/fluticasone in addition to tiotropium (Aaron et al., 2007) did not find "triple" therapy reduced the proportion of patients suffering at least one exacerbation, the primary study endpoint. Despite this, patients receiving "triple" therapy did experience fewer hospitalisations for COPD and for all causes, as well as a clinically significant improvement in their quality of life [evidence level II].

Although RCTs have not found a benefit for triple therapy on mortality, a retrospective cohort study of patients with COPD in the Veterans Affairs health care system found the regimen of tiotropium and inhaled corticosteroids and long-acting beta-agonists was associated with 40% reduced risk of death (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.45-0.79) compared with inhaled corticosteroids and long-acting beta-agonists. (Lee et al., 2009) Triple therapy was also associated with reduced rates of COPD exacerbations (HR, 0.84; 95% CI, 0.73-0.97) and COPD hospitalizations (HR, 0.78; 95% CI, 0.62-0.98)

(Lee et al, 2009) [evidence level III-2].

## O5. Inhaler technique and adherence

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. Correct inhaler technique is essential for the optimal use of all inhaled medications (Melani et al., 2011) [evidence level I]. Ease of operating and dose preparation were rated as being the most important inhaler features leading to higher patient satisfaction and fewer critical errors in a randomised, open-label, multicentre, cross-over study of two inhaler devices (van der Palen et al., 2013) [evidence level II]. The National Asthma Council Australia has produced a number of “how-to” video clips instructing patients how to use their inhalers. These are available on their website at <http://www.nationalasthma.org.au/managing-asthma/how-to-videos/using-your-inhaler>. Lung Foundation Australia’s resource, *Better Living With COPD: A Patient Guide* contains an Inhalation devices chapter which can be accessed at <http://lungfoundation.com.au/wp-content/uploads/2014/02/08.-Using-your-inhalation-devices.pdf>. 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. (NHS Centre for Reviews and Dissemination, 2003) The range of devices currently available, the products and dosage, as well as their advantages or disadvantages, are listed in Appendix 2. Brief counselling; monitoring and feedback about inhaler use through electronic medication delivery devices; and multi-component interventions consisting of self-management and care co-ordination delivered by pharmacists and primary care teams have been shown to improve medication adherence. (Bryant et al., 2013)

## O6. Non-pharmacological interventions

### O6.1 Physical activity

Many people with COPD are markedly inactive in daily life. (Pitta et al., 2005) Regular physical activity is recommended for all individuals with COPD (Garcia-Aymerich et al., 2006, Garcia-Aymerich et al., 2009) [evidence level III-2]. In one cohort study of 341 patients hospitalised for the first time with a COPD exacerbation, regular physical activity was related to a higher DLCO, expiratory muscle strength, exercise capacity (6MWD) and VO<sub>2</sub> peak as well as to lower levels of systemic inflammation, after adjusting for confounders (Garcia-Aymerich et al., 2009) [evidence level III-2]. In 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 (Garcia-Aymerich et al., 2006) [evidence level III-2].

### O6.2 Exercise training

Exercise training is considered to be the essential component of pulmonary rehabilitation. (Spruit et al., 2013), (Ries et al., 2007) 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 (Lacasse et al., 2006) [evidence level I]. Improvements in muscle strength and self-efficacy have also been reported. (Ries et al., 2007) Exercise training also improves exercise tolerance in individuals with mild disease. (Chavannes et al., 2002) Exercise training may confer a significant but small increase in physical activity (Cindy Ng et al., 2012) [evidence level III-3].

Inspiratory muscle training (IMT), performed in isolation using a threshold loading device or target-flow resistive device at loads equal to or greater than 30% of an individual’s maximum inspiratory pressure generated against an occluded airway (P<sub>I</sub>max) has been shown to produce short-term gains in inspiratory muscle strength and endurance, reduce dyspnoea, improve functional exercise capacity (6 or 12 minute walk distance) and improve health-related quality of life in patients with COPD (Gosselink et al., 2011) [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 patients with COPD. (Gosselink et al., 2011) At present, the evidence does not support the routine use of IMT as an essential component of pulmonary rehabilitation. (Ries et al., 2007)

Some very disabled patients are shown how to reduce unnecessary energy expenditure during activities of daily living. (Spruit et al., 2013) Some patients who experience marked oxygen desaturation on exertion may benefit from ambulatory oxygen during exercise training and activities of daily living. (see section P10 Oxygen therapy).

Maintenance of regular physical activity is essential for continuing the benefits from the initial training program. (Ries et al., 2007) 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.(Brooks et al., 2002) 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. (Spruit et al., 2013),(Ries et al., 2007) Although most of the evidence for the benefits from exercise training has been gained from supervised programs that involved land-based exercise training, a Cochrane review provides limited evidence from randomized controlled trials conducted in a small number of patients with GOLD II and III COPD that water-based exercise may confer short-term benefits in exercise capacity and quality of life ((McNamara et al., 2013)) [evidence level I].

### **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 is often included with exercise training as part of a comprehensive pulmonary rehabilitation program(Ries et al., 2007)[evidence level III-2]. Delivering COPD-specific information in a didactic style is unlikely to be beneficial and therefore is not recommended.(Blackstock and Webster, 2007) Providing information and tools to enhance self-management in an interactive session is more effective than didactic teaching. (Lorig et al., 1999),(Blackstock and Webster, 2007)

A systematic review of self-management education for COPD(Effing et al., 2007) 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 corticosteroids 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. Several more studies have not shown any benefit from self-management interventions. (Bucknall et al., 2012, Bischoff et al., 2012) One study found excess mortality in the self-management group.(Fan et al., 2012) The differences may be related to differences in the study populations, study context and extent of self-management support provided.

The single most important intervention is assistance with smoking cessation.(NHLBI/WHO Workshop Report, April 2001) 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.(NHLBI/WHO Workshop Report, April 2001),(Spruit et al., 2013),(Morgan et al., 2001)

#### **O6.3.1 Psychosocial support**

Support groups may provide people with COPD and their carers with emotional support, social interaction, and new knowledge and coping strategies, although studies specifically evaluating the benefits of these groups for improving quality of life and psychological well-being are yet to be conducted. Pulmonary rehabilitation provides a good opportunity to initiate support group attendance. 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. A list of Patient Support Group names and locations can be accessed via Lung Foundation Australia's website at <http://lungfoundation.com.au/patient-area/patient-support/patient-support-groups/>. Contact details can be obtained from Lung Foundation Australia's Information and Support Centre (free-call 1800 654 301). In New Zealand, contact the Asthma Foundation (phone +64 4 499 4592; Internet address, <http://www.asthmanz.co.nz>).

People with COPD are vulnerable to developing symptoms of anxiety and depression, which then worsen quality of life and disability(Xu et al., 2008, Eisner et al., 2010b). Pulmonary rehabilitation has been associated with short-term reductions in anxious and depressive symptoms.(Coventry and Hind, 2007, Coventry et al., 2013) Additional intervention by mental health specialists will be required for clinically significant symptoms of anxiety or depression(Livermore et al., 2010).

## 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, behaviour change, nutritional intervention and psychosocial support (Spruit et al., 2013). An online toolkit is available to assist health professionals to implement a Pulmonary Rehabilitation Program. See [www.pulmonaryrehab.com.au](http://www.pulmonaryrehab.com.au)

Pulmonary rehabilitation is one of the most effective interventions in COPD (Lacasse et al., 2006), (Ries et al., 2007) and has been shown to reduce symptoms, disability and handicap, reduce hospitalisation (Griffiths et al., 2000, Griffiths et al., 2001) and to improve function by:

- improving peripheral muscle function, cardiovascular fitness, muscle function and exercise endurance (Lacasse et al., 2006, Ries et al., 2007, Troosters et al., 2005);
- enhancing the patient's emotional function, self-confidence and coping strategies, and improving adherence with medications; (Morgan et al., 2001, Lacasse et al., 2006)
- improving mood by controlling anxiety and panic, decreasing depression, and reducing social impediments (Ries et al., 2007), (Harrison et al., 2012).

Pulmonary rehabilitation should be offered to patients with COPD, irrespective of the severity of their disease and can be relevant for people with any long-term respiratory disorder characterised by dyspnoea. (Spruit et al., 2013), (Ries et al., 2007) Patients with COPD, of all MRC grades, gain significant benefit from rehabilitation. (Evans et al., 2009), (Altenburg et al., 2012) However, those with the most severe disability, i.e. those who are breathless at rest or on minimal activity (MRC grade 4 and 5) are more likely to have difficulties attending out-patient programs due to problems with transport. (Sabit et al., 2008) Exercise programs alone have clear benefits, (Lacasse et al., 2006) while the benefits of education or psychosocial support without exercise training are less well documented. (Ries et al., 2007), (Spruit et al., 2013) 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. (Spruit et al., 2013) (Ries et al., 2007) 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 (Ries et al., 2007) [evidence level II].

A list of pulmonary rehabilitation programs known to Lung Foundation Australia can be accessed at <http://lungfoundation.com.au/patient-area/resources/pulmonary-rehabilitation/pulmonary-rehabilitation-programs-2/>. The individual contact details can be obtained by calling the Lung Foundation's Information and Support Centre (free-call 1800 654 301).

## O6.5 Breathing exercises

A variety of breathing exercises are used in people with COPD. The aim of these exercises is to reduce dyspnoea by altering respiratory muscle recruitment, reducing lung hyperinflation, improving the functioning of the respiratory muscles and optimising thoraco-abdominal motion.

A Cochrane Review of 16 studies involving a total of 1233 individuals with stable COPD (Holland et al., 2012) evaluated the effects of a variety of breathing exercises alone, or together with other interventions, on the primary outcome measures of dyspnoea, exercise capacity and health-related quality of life. The review found some evidence that breathing exercises (pursed lip breathing, diaphragmatic breathing, yoga involving pranayama timed breathing techniques) performed for between 4 and 15 weeks when compared to no breathing exercises improved exercise capacity as measured by 6-minute walking distance [evidence level I/II] but had inconsistent effects on dyspnoea or HRQoL. Mixed results were found when breathing exercises were compared with other techniques, namely inspiratory or expiratory muscle training, or whole body exercise training, or when combined with another intervention. Computerised ventilation feedback was less effective than exercise training for improving exercise endurance [evidence level III-2] and when combined with exercise training did not confer any additional benefits in dyspnoea compared to exercise training alone [evidence level III-2]. No significant adverse effects were reported in the studies. A major limitation of the studies was that assessor blinding could only be determined in two studies.

The findings of this review do not support the widespread application of breathing exercises in the management of people with COPD. However, breathing exercises may have a role to improve exercise tolerance in selected individuals with COPD who are unable to undertake exercise training.

## O6.6 Chest physiotherapy (Airway clearance techniques)

Airway clearance techniques are only indicated for patients with COPD who have evidence of sputum. This is likely to include individuals who have the clinical features of chronic bronchitis, those with co-existent bronchiectasis and some patients during an acute exacerbation.

The aims of airway clearance techniques in patients with COPD are to assist sputum clearance in an attempt to reduce symptoms, slow the decline in lung function, reduce exacerbation frequency and hasten the recovery from exacerbations.

A variety of techniques are available. These include the active cycle of breathing techniques (ACBT), (a cycle of breathing control, thoracic expansion exercises and the forced expiration technique), conventional chest physiotherapy (defined as any combination of gravity-assisted drainage, percussion, vibrations and directed coughing / huffing), positive expiratory pressure (PEP) therapy, devices that combine positive expiratory pressure and an oscillatory vibration of the air within the airways (Flutter® or Acapella®) and autogenic drainage (AD). Autogenic drainage is a technique that is based on the principle of achieving the highest possible airflow in different generations of bronchi, while preventing early airway closure, via the use of controlled tidal breathing. Short-acting inhaled bronchodilators prior to treatment may assist with sputum clearance in some patients.

A Cochrane systematic review (Osadnik et al., 2012) of 19 studies of airway clearance techniques (ACTs) in patients with stable COPD found evidence from single studies suggesting that ACTs may reduce the need for hospital admission and improve health-related quality of life [evidence level II]. It is possible that ACTs may also enhance sputum clearance and exercise tolerance, and reduce the longer-term need for antibiotics [evidence level II] although further research is required. The trials included in the review were generally of small sample size and the ability to pool data for meta-analyses was limited due to heterogeneity of outcome measures and inadequate reporting from cross-over studies.

It is unlikely that one airway clearance technique is appropriate or superior for all patients with COPD. The choice of technique depends on the patient's condition (e.g. extent of airflow limitation, severity of dyspnoea), sputum volume and consistency, the effects of the different techniques on lung volumes, expiratory flow and dynamic airway compression, presence of co-morbid conditions, cognitive status of the patient and acceptability of the technique to the patient especially where long-term treatment is required. (Holland and Button, 2006).

## O6.7 Smoking cessation

While smoking cessation has long been known to reduce the rate of decline of lung function (see section P1.1), there is evidence it also has short-term benefits on lung function and quality of life. In a randomised controlled trial of varenicline. (Tashkin et al., 2011b) participants who continuously abstained from smoking compared to those who relapsed, had higher post-bronchodilator FEV1 at weeks 12 (mean 121.8 vs. 37.9 mls,  $p < 0.007$ ) and 24 (mean 58.4 vs. -19.1 mls,  $p = 0.07$ ) when compared to baseline measurements, although the difference at the latter time point was not statistically significant. Similarly, those who abstained, when compared to those who relapsed, had a greater improvement in the total clinical COPD questionnaire score at 12 weeks (mean -1.04 vs -0.53,  $p < 0.0001$ ), and this significant benefit was also seen at 24 and 52 weeks. Benefits at all time points were also found for the domain scores of respiratory symptoms, functional status and mental state.

## O6.8 Nutrition

Nutritional management of COPD is complex, as both malnutrition and obesity are highly prevalent and both contribute to the patient's morbidity and mortality risk. In addition, poor eating habits, sedentary lifestyle, smoking and corticosteroid use can lead to poor nutritional status in COPD, with deficiencies in various nutrients such as vitamins and minerals, fatty acids and amino acids. The randomised controlled trials (RCTs) that have been conducted with the aim of achieving a healthy weight, improving nutritional status and functional outcomes in COPD are discussed below.

Malnutrition: Low body weight and/or low fat free mass (FFM) is common in COPD, particularly in those patients with severe disease, due to an inadequate nutritional intake compared to energy expenditure. Energy intake may be reduced due to breathlessness during eating, hyperinflation of lungs causing pressure on the stomach and loss of appetite induced by drugs. (Sridhar MK, 2006) At the same time, energy demands may be increased due to the energy costs of breathing and the metabolic costs of respiratory tract infections. (Sridhar MK, 2006) As a result, low BMI and loss of FFM are common in COPD patients and this increases COPD mortality risk, being inversely associated with respiratory and peripheral muscle function, exercise capacity and health status. (Vestbo et al., 2006, Schols et al., 2005) Two meta-analyses have shown that high calorie nutritional support has small, yet beneficial effects in COPD, particularly in those who are undernourished. A systematic review which included 13 RCTs of nutritional support conducted a meta-analysis that showed a pooled increase in mean weight, which was greatest in undernourished patients [1.94 (95%CI 1.43-2.45) kg]. There were also increases in grip strength 5.3% ( $p < 0.05$ ) and small effects on fat free mass and skin fold thickness (Collins et al., 2012) [evidence level I]. A Cochrane Review updated in 2012 also demonstrated in a meta-analysis of data from 17 RCTs, that nutritional therapy resulted in body weight gain in undernourished patients [1.65 (95%CI 0.14-3.16) kg] and improved FFM index and exercise tolerance (6MWD) in all patients

(Ferreira et al., 2012) [evidence level I]. Hence high calorie nutritional supplements should be considered in COPD, particularly those who are malnourished.

**Obesity:** At the other end of the spectrum, obesity is becoming increasingly prevalent in COPD. Obesity complicates COPD management and in addition to the negative metabolic consequences, is associated with decreased expiratory reserve volume (ERV) and functional residual capacity (FRC), increased use of inhaled medications, increased dyspnoea and fatigue, decreased health related quality of life and decreased weight bearing exercise capacity. (Cecere et al., 2011, Ramachandran et al., 2008, Ora et al., 2009) Despite these negative effects, obesity has been associated with reduced mortality risk in severe COPD, (Landbo et al., 1999) which may be due to a reduction in static lung volumes (Casanova et al., 2005) and /or the increase in FFM (Poullain et al., 2008) that occurs in obesity due to over-nutrition and increased weight bearing. Weight loss interventions have not been tested in COPD to date and no recommendations are currently available. Considering the improved prognosis for severe COPD patients with increasing BMI, weight loss strategies need to be considered with caution.

**Other nutritional interventions:** Various other nutritional interventions have been evaluated in COPD. However to date, the level of evidence supporting these interventions is level II or less.

**Fruit and vegetables:** Fruit and vegetables are recognised as being part of a healthy diet as they are low in energy, yet dense in nutrients such as vitamins and minerals, fibre and phytochemicals. Two RCTs manipulating fruit and vegetable intake have been conducted in COPD. A 12 week study in 81 COPD subjects showed no effect of a high fruit and vegetable intake on FEV<sub>1</sub>, systemic inflammation or airway oxidative stress. (Baldrick et al., 2012) However, a 3 year study in 120 COPD patients revealed an improvement in the high fruit and vegetable group compared to the control group (Keranis et al., 2010), suggesting that longer term intervention provides a therapeutic effect [evidence level III-1].

**Vitamin E:** Vitamin E is a nutrient with antioxidant and anti-inflammatory properties. The ability for vitamin E to reduce biomarkers of oxidative stress in COPD has been demonstrated in one RCT (Daga et al., 2003), but not another. (Wu et al., 2007) In a large-scale RCT (Women's Health Study, n=38597), the risk of developing chronic lung disease over a 10 year supplementation period was reduced by 10% in women using vitamin E supplements (600 IU on alternate days) [evidence level II].

**Ome.g.a-3 fatty acids:** Ome.g.a-3 fatty acids have been demonstrated to have diverse anti-inflammatory effects. Two RCTs have examined the effect of ome.g.a-3 polyunsaturated fatty acids (PUFA) in COPD. One RCT randomised 32 COPD subjects to supplementation with 0.6g ome.g.a-3PUFA per day combined with low intensity exercise or a control group for 12 weeks. They reported an improvement in weight, exercise capacity, quality of life and inflammation in the ome.g.a-3PUFA/ exercise group compared to controls. (Sugawara et al., 2010) The other study compared the effects of 8 weeks supplementation with 3g ome.g.a-3PUFA/day versus a placebo in 102 COPD subjects undergoing pulmonary rehabilitation. They reported an increase in exercise capacity in the ome.g.a-3PUFA group compared to the placebo group, but there were no effects on muscle strength, FEV<sub>1</sub> or inflammation. (Broekhuizen et al., 2005) Hence ome.g.a-3PUFA supplementation may be a useful adjunct to COPD rehabilitation programmes [evidence level II].

**Vitamin D/ calcium:** Vitamin D regulates calcium homeostasis and bone metabolism, as well as having roles in immune function, inflammation, airway remodelling and muscle strength. Vitamin D is frequently deficient in COPD due to factors including the use of oral corticosteroids, smoking, poor diet and reduced exposure to sunlight due to physical limitations. Vitamin D deficiency was associated with lower lung function and more rapid decline in FEV<sub>1</sub> among smokers in a cohort of elderly men followed for 20 years (Lange et al., 2012) [evidence level III-2]. As a result, osteoporosis is highly prevalent in COPD; in 658 COPD patients in the TORCH study, 23% were osteoporotic and 43% osteopenic. (Ferguson et al., 2009) While there are no COPD-specific treatment guidelines for osteoporosis, standard treatment guidelines apply, with patients using corticosteroids requiring treatment according to the guidelines for management of corticosteroid-induced osteoporosis, including daily calcium intake of 1200-1500 mg/day and vitamin D doses of 800-1000 IU per day. (Grossman et al., 2010) In an RCT using high-dose vitamin D (100,000 IU per month) administered over 1 year to 186 COPD patients, there was no improvement in exacerbation frequency, lung function, quality of life or mortality rate compared to placebo. (Lehouck et al., 2012) However, in the same trial, this vitamin D regimen resulted in an improvement in inspiratory muscle strength and oxidative metabolism compared to the placebo group, in patients undergoing pulmonary rehabilitation (Hornikx et al., 2012) [evidence level II].

**Amino Acids:** Amino acids are the building blocks of protein and hence an integral component of muscle tissue. Various types of amino acids and their derivatives have been assessed in intervention trials in COPD. In a 12 week RCT in 88 COPD outpatients, those who received essential amino acid supplementation had an improvement in FFM, muscle strength, physical performance and St George Respiratory Questionnaire (SGRQ) compared to placebo (Dal Negro et al., 2010) [evidence level II]. Another RCT in 28 COPD patients examined outcomes following 12 weeks pulmonary rehabilitation, in subjects with or without essential amino acid supplementation, including 5g/day branched chain amino acids. Body weight and FFM increased in the supplemented group compared to controls (Baldi et al., 2010) [evidence level III-2]. Whey protein, rich in the amino acid cysteine and other essential amino acids, was trialled in a 16 week RCT in COPD subjects who were undergoing exercise training for the last 8 weeks of the intervention. This resulted in increased exercise capacity and quality of life compared to placebo, but no changes in inflammation (Lavolette et al., 2010) [evidence level II]. In a 6 week RCT in 16 COPD patients, the amino acid derivative L-carnitine was administered concurrent with pulmonary rehabilitation and resulted in improved exercise tolerance and inspiratory muscle strength compared to the placebo group (Borghi-Silva et al., 2006) [evidence level II]. Conversely, the amino

acid derivative creatine, has been shown in meta-analyses to have no effect on muscle strength, exercise tolerance or SGRQ in COPD (Al-Ghimlas and Todd, 2010) [evidence level I]. In summary, based on level II evidence, essential amino acids, whey protein and L-carnitine may be beneficial in COPD, particularly when combined with exercise training.

Anabolic steroids: While anabolic steroids are not diet-derived, they have a potential role in FFM accretion. In patients with COPD with weight loss, anabolic steroids have been shown to increase body weight and lean body mass but have little or no effect on exercise capacity (Yeh et al., 2002, Weisberg et al., 2002) [evidence level II].

In summary, level I evidence exists for the use of high calorie nutritional supplementation in COPD, to achieve body weight gain, improve FFM index and exercise tolerance (6MWD), with results most significant for subjects who are undernourished. Benefits have been demonstrated for increasing fruit and vegetable intake and supplementing with n-3 PUFA, vitamin E, vitamin D, essential amino acids, whey protein and L-carnitine in COPD, particularly when the supplements are used in combination with a pulmonary rehabilitation programme. However, level I evidence supporting the use of these other interventions does not yet exist and further research is needed to confirm efficacy.

Eating strategies

For all COPD patients the goal of nutritional management is to eat a balanced diet and to achieve and maintain a healthy weight. Healthy eating means choosing a variety of foods from each of the five food groups every day, in suitable proportions including: vegetables and legumes/beans; fruit; grain foods, mostly whole grain varieties, such as breads, cereals, rice and pasta; lean meats and poultry, fish, e.g. salmon, tofu, nuts and legumes; and dairy products such as milk, yoghurt and cheese. At the same time, foods that are high in saturated fat, sugar and sodium, such as highly processed and takeaway foods, should be limited.

To prevent dyspnoea while eating various strategies have been recommended:

- Clear the airways of mucus before eating
- If supplemental oxygen is used, make sure this is worn while eating
- Avoid eating large meals, instead eat small nutritious meals and snacks more frequently
- Avoid drinking with meals
- Eat slowly
- Choose softer foods that are easier to chew and swallow, e.g. mashed potato, soups, bananas
- Limit foods that can cause bloating, e.g. beans, onions, cauliflower, soft drinks
- Rest for at least 15-20 minutes after eating in an upright position
- In patients who are underweight, protein and calorie intake can be boosted using high energy, nutrient-rich foods that are easily accessible, such as milk powder, cheese, cream, custard, peanut butter and milkshakes or a nutritionally complete oral supplement (e.g. Sustagen)
- Referral to a dietitian for individual advice may be beneficial

Other tips to avoid aspiration can be found in **O7.5 Aspiration**

## **O6.9 Complementary and alternative therapies**

A systematic review by Guo (Guo et al., 2006) concluded there was no clear evidence supporting the effectiveness of herbal medicines for treating COPD.

There is some evidence that acupuncture may reduce exertional dyspnoea and improve exercise tolerance in people with moderate to severe COPD [evidence level II]. One placebo-controlled double blinded randomised trial (n=68), carried out in Japan (Suzuki et al., 2012), compared acupuncture applied once a week for 12 weeks and sham acupuncture. Eleven standardised acupuncture points, including those close to the respiratory accessory muscles, were used with treatment lasting 50 minutes each session. Compared to sham acupuncture, real acupuncture reduced dyspnoea at the end of a 6MWT by -3.58 points (95% CI -4.27 to -2.90) on the Borg 0-10 dyspnoea scale and improved 6MWD by 46 metres in the treatment group when compared to the sham acupuncture group. A possible mechanism proposed for the benefits was an improvement in rib cage mobility and accessory muscle function due to suppressed electromyogram activity of the accessory muscles by the acupuncture. Further studies are required to evaluate the effects of acupuncture and to determine whether any longer-term benefits of treatment occur.

## O7. Comorbidities

Optimal management of any individual patient with COPD must include careful management of comorbidities and anticipation of increased risks associated with those comorbidities in the presence of COPD. An American population based, nationally representative survey of almost 15,000 people demonstrated that patients with self reported COPD have significantly higher prevalence of important medical co-morbidities.(Schnell et al., 2012) Higher prevalence of cardiac disease, stroke, diabetes, depression, poly-pharmacy and mobility problems were reported.

### O7.1 Increased risks from comorbidities in the presence of COPD

Using a large dataset generated from 311 general practices in the UK, Feary et al(Feary et al., 2010) found COPD was associated with increased risks of cardiovascular disease (OR 4.98, 95% CI 4.85 to 5.81), stroke (OR 3.34, 95% CI 3.21 to 3.48) and diabetes mellitus (OR 2.04, 95% CI 1.97 to 2.12). In the follow-up analyses, after adjusting for confounding by sex and smoking status and stratifying for age, the greatest increase in the rate of acute arteriovascular events was found in the youngest age groups. Further supporting these findings, a prospective study examining in hospital mortality in patients with acute ST segment elevation myocardial infarction found that COPD was a strong independent risk factor for death (6.3% Vs 3.4% P=0.006). (Wakabayashi et al., 2010)

### O7.2 Cardiac disease

COPD patients possess an increased burden of cardiovascular disease (CVD), cardiac arrhythmia and heart failure when compared to the normal population . In Feary’s study of 1,204,100 patients who were followed for a median of 895 days in the primary care setting in the United Kingdom, cross-sectional analysis demonstrated “physician-diagnosed” COPD was associated with increased risk of CVD (OR 4.98, CI 4.85 to 5.81) and stroke (OR 3.34, CI 3.21 to 3.48) after adjustment for age, gender, smoking status, socioeconomic measures, and other comorbidities. In addition, COPD was associated with increased rates of first myocardial infarction (MI) (HR 10.34, CI 3.28 to 32.6), and stroke (HR 3.44, CI 0.85 to 13.84), stratified by age and adjusted for gender and smoking status. Significance was maintained after sensitivity analysis was conducted for possible misclassification of smoking status and COPD diagnosis(Feary et al., 2010) [evidence level III-2]. A retrospective cross-sectional study corroborated these findings, using a database representative of 1.5% of the Italian general practice population and ICD-9 diagnostic codes; diagnosis of COPD, was associated with significantly increased risk of contemporaneous CVD and hypertension. The relationship was even stronger in never smokers(Cazzola et al., 2012) [evidence level III-2].

CVD is an important cause of mortality and hospital presentations in COPD, even affecting those with mild disease. In addition to the high individual prevalences of COPD and CVD, these diseases share conventional risk factors of advanced age, smoking, low socioeconomic status (SES) and sedentary lifestyle. Systemic inflammation, autonomic dysregulation, hypoxia, acidosis and haemodynamic derangements are likely to also contribute.(Fuschillo et al., 2012) Independent of smoking and other risk factors, impaired lung function per se is a major risk factor for CVD and arrhythmia (on par with hypercholesterolaemia), with the relationship being strongest for fatal events (Hole et al., 1996)[evidence level III-2]. Increased arterial stiffness, independent of endothelial vasodilation and fibrinolytic responses, has been proposed as one potential mechanism for this excess of CVD (Maclay et al., 2009). [evidence level III-2].

Medications used in the treatment of COPD also have potential to impact on cardiac morbidity and mortality. However, a post-hoc analysis of cardiovascular adverse event (CAE) data from the TORCH study(Calverley et al., 2010) [evidence level II], a randomised, double-blind, multicentre study comparing combination fluticasone/salmeterol (SFC), the individual drug components and placebo in 6,184 stable moderate to severe COPD patients, did not demonstrate any increased cardiovascular risk from salmeterol at the standard dose used in the study. The study was actually powered to detect a difference in survival, and the primary TORCH paper(Calverley et al., 2007) [evidence level II] had already reported no increased risk of cardiac death attributable to salmeterol over the three years of the study. Once results were adjusted for differential treatment exposure between groups, the risk of CAE did not significantly differ between the treatment groups, with the lowest event rate seen in the SFC group. However, CAEs were not objectively documented and, surprisingly, no adverse effect of current smoking was seen. The study reported a signal for an association of short-acting antimuscarinic medication (SAA) with CAEs, but confounding by disease severity was likely.

Markers of cardiac involvement during acute exacerbation of COPD (AECOPD) may be an important determinant of short-term prognosis. In a study of 250 consecutive admissions with AECOPD and no evidence of acute cardiac disease over 12 months, elevated NT-pro BNP >220 pmol/L and troponin T >0.03 were present in 27% and 16.7% subjects and predicted 30 day mortality (OR 9, CI 3.1-26.2) and (OR 6.3, CI 2.4 – 16.5), respectively, after adjustment for other predictors of acute mortality. Elevated troponin T level lost significance with both cardiac biomarkers included in the model, although the mortality association was additive for subjects in whom both biomarker levels were elevated(Chang et al., 2011) [evidence level III-2].

Preliminary research suggests that cardiac pathology contributes to a proportion of AECOPDs. A small study(Bhatt et al., 2012)

[evidence level III-2] investigated a potential role for arrhythmia in AECOPD; comparing ECG indices during AECOPD with stable state. They reported that P wave duration was more variable during exacerbation. Moreover, “frequent exacerbator patients” (defined as two or more AECOPDs within 12 months) had increases in ECG PR interval during stable state compared with “infrequent exacerbators”. Although methodology was not robust, the results probably justify further research into this issue. A retrospective single centre cohort study (Abusaïd et al., 2009) [evidence level III-2] proposed a contributory role for diastolic dysfunction (DD) in AECOPD, suggesting that DD was associated with prolonged length of hospital stay (4.02 versus 3.24 days,  $p=0.005$ ) and increased frequency of AECOPD hospitalisation (1.28 versus 0.67 per patient year,  $p=0.0067$ ) in the absence of traditional precipitating factors.

Donaldson et al (Donaldson et al., 2010) sought to quantify the increased risk of CAEs associated with AECOPD. Using self-controlled case series methodology, they identified 25,857 COPD patients and their CAEs (524 MIs in 426 patients and 633 ischaemic strokes in 482 patients) using health care database diagnostic codes and defining AECOPD by receipt of systemic corticosteroid course (at minimum daily dose) and/or specified antibiotics. Comparing CAE incidence during the period immediately after AECOPD with that in stable state and adjusting for seasonality, they demonstrated increased risk for MI (RR 2.27, CI 1.1 to 4.7) in the five days following AECOPD onset, if combined antibiotics and steroids were required and increased risk for stroke (RR 1.26, CI 1.0 to 1.6) for 49 days, for AECOPD requiring antibiotics only [evidence level III-2].

Two studies have attempted to evaluate the extra morbidity burden conferred by heart disease in COPD [evidence level III-2]. De Miguel Diez (de Miguel-Diez et al., 2010) recruited patients meeting diagnostic criteria for stable COPD from the Spanish primary health care setting and assessed chronic morbidity and health resource utilisation according to the presence of ICD-9 codes for heart disease. Of 9,390 COPD patients, 18.8% had documented heart disease. Compared to patients without heart disease this group had worse lung function, worse QoL, required more respiratory medications, consumed more health resources and generated greater expenses - differences which were all statistically significant. The authors identified admission duration as a major contributor to increased costs in these patients [evidence level III-2]. In the study by Patel’s group (Patel et al., 2012), data from the London Cohort (1995 – 2009), comprising prospectively collected exacerbation data via symptom diaries from 386 subjects with COPD (as defined by spirometry) and at least 12 months’ diary data. Health status assessment occurred whilst in stable phase and comparison was made regarding frequency and duration of AECOPD between patients with and without ischaemic heart disease (IHD). The 16% of the cohort with IHD scored worse on QOL assessment (St George Respiratory questionnaire), MRC dyspnoea scale and six minute walk distance. There was no difference in frequency of respiratory exacerbations or the need for antibiotics and systemic corticosteroid therapy. However, subjects with IHD recovered more slowly and so endured more days with increased levels of symptoms. The subjects did not differ in COPD treatments received, but the authors provided no information on treatments received for IHD [evidence III–2].

Conversely, the prevalence of clinically diagnosed COPD was 12% among 3,438 patients with first MI occurring between 1979 and 2007 in Minnesota, USA. COPD prevalence increased significantly over time, and was associated with increased mortality (adjusted HR 1.3, CI 1.1 to 1.54) independent of age, traditional indicators of poor prognosis and comorbidities. The association of COPD with survival remained unchanged over time, despite the overall decline in mortality after MI (Bursi et al., 2010) [evidence level III–2].

### **O7.2.1 Heart failure**

The diagnosis of heart failure coexisting with COPD is complicated by symptom overlap and the technical challenges of echocardiography in COPD. The natriuretic peptides, including BNP and NT-pro BNP, can assist in identifying heart failure in the setting of acute breathlessness, but do not exclude comorbid COPD, and currently have an unclear diagnostic role in stable disease. The prevalence of heart failure in COPD patients is estimated at 20-32%. For the converse situation in heart failure, COPD prevalence has been previously quoted as 10-33%. A prospective multicentre substudy (Iversen et al., 2008) [evidence level III-2] of patients admitted with heart failure confirmed COPD in 35% of subjects using spirometry. Self-reported COPD diagnosis had poor sensitivity to identify these individuals. Prevalence of COPD was higher in those heart failure patients with preserved left ventricular ejection fraction (LVEF), but was also substantial in those with reduced LVEF (41% versus 31%,  $p=0.03$ ).

A subgroup study from a multicentre prospective cross-sectional study of CVD (Barr et al.) [evidence level III-2] demonstrates a linear relationship between extent of emphysema and impairment of LV filling, reduction of stroke volume and of cardiac output, without a threshold effect, in “healthy” subjects prospectively assessed for cardiac disease with MRI. Extent of emphysema was quantitatively measured on computerised tomography. A 10% increase in measured emphysema was associated with 4.1mL reduction in left ventricular end diastolic volume (LVEDV) (95% CI -3.3 to -4.9,  $p<0.001$ ), 2.7 mL reduction in stroke volume (95% CI -2.2 to -3.3,  $p<0.001$ ) and 0.19L/min reduction in cardiac output (95% CI -0.14 to -0.23,  $p<0.001$ ). The same association was not present for LVEF. Smoking status was an effect modifier, with a greater effect seen for current smokers. Similar relationships were obtained for measures of airflow obstruction.

In COPD, heart failure adversely impacts on morbidity and prognosis. Two studies further clarify the relationship. A

prospective cohort study (Boudestein et al., 2009) [evidence level III-2] sought to quantify heart failure and its prognostic implications in 405 Dutch general practice patients identified as having COPD. Extensive diagnostic testing revealed occult heart failure in 20.5%; half of which half was systolic, half diastolic and none was cor pulmonale. Similar proportions were found in the subset of 244 patients meeting GOLD criteria for COPD. Not unexpectedly, comorbid heart failure proved a strong predictor of all cause mortality over the mean follow up duration of 4.2 years for the whole cohort (adjusted HR 2.1, CI 1.2-3.6, p=0.01) and for “GOLD COPD subjects” (adjusted HR 2.0, CI 1.0-3.7, p=0.04). It was also a significant risk factor for death from respiratory failure and for respiratory admissions in “GOLD COPD” patients. Secondly, a retrospective single centre cohort study (Abusaid et al., 2009) [evidence level III-2] proposed a contributory role for diastolic dysfunction (DD) in acute exacerbation of COPD (AECOPD), suggesting that DD was associated with prolonged length of hospital stay (4.02 versus 3.24 days, p= 0.005) and increased frequency of AECOPD hospitalisation (1.28 versus 0.67 per patient year, p=0.0067) in the absence of traditional precipitating factors. Since COPD and heart failure present with similar symptoms and frequently do coexist, the clinical implication is that the opportunity for intervention will be missed unless both diagnoses are specifically sought using careful clinical assessment in conjunction with appropriately directed investigations.

### O7.2.2 Safety of beta-blockers

Beta-blockers have well established benefits in heart failure and after myocardial infarction and have been long used in coronary artery disease and hypertension, but have been considered contra-indicated in patients with COPD. A Cochrane systematic review identified 20 RCTs of cardio-selective beta-blockers which examined lung function and respiratory symptoms in 278 patients with COPD (Salpeter et al., 2005, Salpeter et al., 2002) [evidence level I]. Eleven studies were of single dose and nine were of prolonged treatment (mean 3.7 weeks, range two days to 12 weeks). The beta blockers included atenolol, metoprolol, bisoprolol, practolol, celiprolol and acebutolol and were used at therapeutic doses. There was no significant overall change in FEV<sub>1</sub>, increase in respiratory symptoms or change in the response to inhaled beta<sub>2</sub> agonists. The authors concluded that cardio-selective beta-blockers were safe and should not be withheld, even in patients with severe airflow limitation. However, even with pooled data the absolute subject numbers were small, and failed to represent minority groups such as females and the elderly. The longest duration included trial was 12 weeks, and so the meta-analysis provides little guidance about long-term safety and potential morbidity of prolonged beta-blocker use in COPD. Mentz et al (Mentz et al., 2013) performed a retrospective analysis of patients admitted with heart failure who had a clinical diagnosis of COPD. The authors found that patients prescribed a beta-blocker had lower 90 day mortality rates than those not prescribed a beta-blocker. They also found that there was no difference in mortality rates between patients prescribed selective and non-selective beta-blockers [evidence level III-2].

Observational studies add reassurance. Five of these report increased survival (Dransfield et al., 2007, van Gestel et al., 2008, Olenchock et al., 2009, Rutten et al., 2010, Short et al., 2011) [evidence level III-2]. In Dransfield's, van Gestel's and Rutten's studies, respective beta-blocker prescription rates for COPD subjects were 17%, 38% and 30%. In Olenchock's study, 66% of reactive airways disease subjects received beta-blockers within 24 hours and 77% received them at discharge. All studies adjusted for potential confounders, and only Olenchock's group did not attempt additional adjustment for beta-blocker prescribing propensity. All groups reported reduction in mortality associated with beta-blocker use: for Dransfield's group, reduced in-hospital mortality (OR 0.39, 95% CI 0.14 to 0.99), for van Gestel's group, reduced 30 day mortality (OR 0.37, 95% CI 0.19 to 0.72) and long term mortality (OR 0.73, 95% CI 0.6 to 0.88), for Olenchock's group reduced in hospital mortality (OR 0.52, p <0.001) for receipt of beta-blocker within 24 hours and for Rutten's group, reduced long term mortality (HR 0.68, 95% CI 0.56 to 0.83) and reduced AECOPD (HR 0.71, 95% CI 0.6 to 0.83). Short's COPD database study of 5,977 subjects reported a reduction in all-cause mortality (HR 0.78, CI 0.67 to 0.92) with beta-blockers being associated with mortality benefit in all groups when patients were stratified according to severity using their inhaled COPD treatment. In this study beta-blockers did not worsen lung function decline in the 2,712 subjects for whom serial measures were available. Reduced risk of cardiac death, respiratory death, oral corticosteroid courses and respiratory-related hospital admissions related to beta-blocker use were also reported.

Acknowledging that, beyond improving survival, treatments used in COPD patients must not impair QOL. van Gestel's 2009 study (van Gestel et al., 2009) [evidence level III-2] sought reasons for suboptimal beta-blocker prescription in terms of QOL. The surviving 469 COPD patients of their vascular surgery cohort were subsequently assessed via health-related QOL questionnaire (SF-36) at median follow up of 6.4 (2.9 to 9.3) years. A 70% response rate was achieved. Although 71% of patients were receiving beta-blockers at follow up, compared to 59% at baseline, neither beta-blocker treatment at baseline, nor at follow up, impacted significantly on QOL scores.

### O7.2.3 Statins

Interest in a potential disease-modifying role for HMG CoA reductase inhibitors (statins) in COPD is based upon established survival benefit in CVD as effective lipid-lowering drugs in combination with anti-inflammatory and antioxidant effects. Outcomes of statin treatment in COPD have been reviewed by two groups (Dobler et al., 2009, Janda et al., 2009) Both groups

identified 9 eligible studies. Janda's group identified one additional population-based analysis. Only one RCT was included. All studies reported beneficial outcomes, including decreased all-cause mortality in 3 of 4 trials, decreased COPD-related mortality in 2 of 2 trials and decreased need for respiratory-related urgent care in 2 of 2 trials. Single studies reported decreased exacerbations, intubation, exertional dyspnoea and inflammatory parameters, attenuated lung function decline and increased exercise capacity. The RCT reported improvements in exercise capacity, dyspnoea and indices of inflammation, but no effect on lung function. Another cohort study of patients (Lawes et al., 2012) admitted to public hospitals in New Zealand for acute exacerbations of COPD found that use of a statin prior to admission was associated with a reduction in all cause mortality (HR 0.69, 95%CI 0.58, 0.84) [evidence level III-2]. The most important weaknesses of these reviews are the potential for publication bias and the inherent methodological limitations imposed by the non-interventional study design of the majority of included studies. Despite the likelihood of publication bias, the distinct possibility of COPD misdiagnosis in included studies and the need for better definition of the statin exposure in terms of identifying drugs, dosages, therapy duration and compliance, the positive flavour of the results do warrant further investigation in the form of prospective interventional studies [evidence level II].

#### 07.2.4 Coronary revascularisation procedures

Patients with COPD are at increased risk of death and complications following cardiac surgery [evidence level III-2]. A study identified 1169 patients undergoing coronary artery bypass grafts and/ or valve replacement at one US centre who had preoperative lung function tests (Adabag et al., 2010). Operative mortality was 2% in those with no or mild airflow limitation, compared to 6.7% among those with moderate or severe airflow limitation ( $FEV_1/FVC < 70\%$  and  $FEV_1 < 80\%$  predicted). Postoperative mortality was 3.2 (95%CI 1.6-6.2) fold higher among those with moderate or severe airflow limitation and 4.9 (2.3-10.8) fold higher among those with diffusing capacity  $< 50\%$  predicted. These patients were also more likely to require mechanical ventilation for  $> 48$  hours and stayed longer in intensive care and hospital than those with normal lung function.

COPD and COPD severity as defined by spirometry were also associated with increased mortality (OR 1.79, CI 1.63 to 1.96), cardiac mortality (OR 1.57, CI 1.35 to 1.81) and post-discharge MI (OR 1.3, CI 1.14 to 1.47) after percutaneous coronary intervention in multivariate analysis, despite equivalent procedural success and complication rates (Konecny et al., 2010) [evidence level III-2]. In this study, data prospectively collected for 14,346 patients (2001 COPD and 12345 non-COPD) from a single centre between January 1995 and August 2008 were subjected to retrospective cross-sectional analysis. COPD patients were identified by ICD - 9 diagnostic codes and did possess significantly more manifestations of CVD, including heart failure, than the control group. Unfortunately preoperative lung function data was only available in 60% of the COPD group.

#### 07.3 Osteoporosis

##### Prevent or treat osteoporosis

Patients with COPD are at increased risk for fracture due to the disease itself, the use of high dose corticosteroids and coexisting risk factors such as hypogonadism (induced by corticosteroid therapy itself in high doses in men and women), immobilisation 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. A systematic review by Graat-Verboom (Graat-Verboom et al., 2009) described an overall mean prevalence of osteoporosis of 35.1% (range 9-69%) with increasing odds ratios for osteoporosis associated with  $FEV_1$ , lower BMI and lower fat-free mass index.

Although, there is little evidence of a deleterious effect of inhaled corticosteroid at conventional doses ( $< 2, 200$  mcg/day) on fracture risk, triamcinolone was associated with reduced BMD in the Lung Health Study (Lung Health Study Research Group, 2000) [evidence level II]. In a large study by Ferguson et al (Ferguson et al., 2009) comparing the effects of salmeterol, fluticasone 1000 micrograms daily, the combination, or placebo, there was no increase in decline in bone mineral density over three years in active arms compared with placebo in the subgroup of patients whose bone density was measured [evidence level II]. Australian Guidelines on the prevention and treatment of osteoporosis, including corticosteroid-induced osteoporosis have been published. (Sambrook et al., 2002) Information on the current subsidies relevant to these drugs can be found at <http://www.osteoporosis.org.au/treatment-options> or on the website of the Pharmaceutical Benefits Scheme ([www.pbs.gov.au](http://www.pbs.gov.au)) Higher doses of inhaled corticosteroids are associated with suppressed biochemical markers of remodelling but data on BMD and fractures at these doses are not available (Jones et al., 2002) [evidence level I].

Despite the lack of evidence, management strategies in individuals taking long term corticosteroid 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 (Homik et al., 2000) 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.

#### **O7.4 Sleep related breathing disorders**

COPD has adverse effects on sleep quality, resulting in poor sleep efficiency, delayed sleep onset, multiple awakenings 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  $\beta$ -adrenergic agents. (Phillipson and Bowes, 1986) Intranasal oxygen administration has been shown to improve sleep architecture and efficiency, as well as oxygen saturation during sleep. (Meecham Jones et al., 1995)

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 PaO<sub>2</sub> 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 PaO<sub>2</sub> <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” (McNicholas, 2009) [evidence level III-2]. The prevalence of COPD in unselected patients with OSA is about 10%, while about 20% of patients with COPD also have OSA. (Chaouat et al., 1995) Patients with COPD who also have OSA have a higher prevalence of pulmonary hypertension and right ventricular failure than those without OSA. (Chaouat et al., 1995) Results of a longitudinal observational study suggest that COPD patients with overlapping OSA have higher mortality and more frequent exacerbations of their disease than COPD patients without OSA [evidence level III-2]. CPAP treatment reduced mortality and exacerbation rates (Marin et al., 2010) [evidence level III-2]. 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 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. Some patients with COPD experience disrupted breathing-swallowing co-ordination and may be at risk of aspiration which may also contribute to exacerbations. (Gross et al., 2009) One hospital based case-control study performed swallowing provocation tests by instillation of distilled water into the nasopharynx. Abnormal swallow reflex was associated with more frequent exacerbations of COPD (Terada et al., 2010) [evidence level III-2].

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.

#### **O7.6 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. In a prospective cohort study, gastro-oesophageal reflux symptoms were associated with an increased risk of exacerbation. (Terada et al., 2008) A nested case control study performed on a large primary care dataset found a modest increased risk of a diagnosis of gastro-oesophageal reflux in patients with a pre-existing diagnosis of COPD (RR 1.46 CI 1.19-1.78) (Garcia Rodriguez et al., 2008). 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 H<sub>2</sub>-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.

### **O7.7 Lung cancer**

Lung cancer is a serious health problem in Australia. (Cancer Council Australia, 2004) In 2007, in Australia, lung cancer was the fourth most commonly diagnosed cancer in both males and females (excluding basal and squamous cell carcinoma of the skin), with a total of 9,703 diagnosed. (AIHW & Cancer Australia, 2011) Lung cancer is the leading cause of cancer deaths for both sexes. The occurrence of lung cancer was strongly related to age, with 84% of new lung cancers in males and 80% in females diagnosed in those aged 60 and over. Smoking is the largest single cause of lung cancer, responsible for 90% of lung cancers in males and 65% of lung cancers in females in Australia. Between 1982 and 2007, the incidence rate of lung cancer decreased in males by 32%, but increased in females by 72%, reflecting historical differences in smoking behaviour.

The risk of lung cancer in people who have pre-existing lung disease has been studied using case-control studies, which found an increased risk of lung cancer in people with bronchitis and emphysema, even after correcting for the smoking history. A cohort study of 2,507 patients with COPD followed for 60 months found an incidence of lung cancer of 16.7 per 1000 patient years. The most frequent histological type was squamous cell (44%) followed by adenocarcinoma (38%) and small cell (12%). A diagnosis of lung cancer was associated with less severe GOLD stage, older age, lower BMI and DLCO <80% predicted. (de Torres et al., 2011)

A much larger cohort study performed record linkage of Danish national hospital and cancer registries. The investigators identified 236,494 patients admitted for COPD between 1980 and 2008, who were followed for median of 3.5 years. During the first year of followup, the Standardised Incidence Ratio (SIR) for any cancer was 3.1 (95%CI 3.0-3.2), and lung cancer 8.5 (95%CI 8.2-8.8). The cumulative risks for lung cancer in this COPD cohort after 1, 5 and 10 years were 1.8% (95%CI 1.7-1.9%), 3.6% (95% CI 3.6-3.7%) and 4.9% (4.9%-5.0) respectively (Kornum et al., 2012) [evidence level III-2].

Research has suggested a mechanism for the association, through identification of single-nucleotide polymorphisms (SNPs) on chromosome 15 in the nicotinic acetylcholine receptor subunit genes (CHRNA3 and CHRNA5) that are associated with smoking behaviour and with an increased risk of lung cancer and COPD. (Bierut, 2010) The SNPs on chromosome 15 appear to have an independent effect on disease risk, as if you incorporate the smoking history into the statistical analyses, the genetic variants continue to contribute to lung cancer risk above and beyond the smoking behaviour. (Bierut, 2010)

### **O7.8 Alcohol and sedatives**

Patients with COPD have impaired gas exchange and an exaggerated fall in Po<sub>2</sub> with recumbency and sleep onset. (Meecham Jones et al., 1995), (Chaouat et al., 1995) 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.

### **O7.9 Testosterone deficiencies and supplementation**

Observational studies in COPD patients have revealed reduced total testosterone levels compared with matched controls [WMD -3.21nmol/L (95%CI -5.18 to -1.23)]. (Atlantis et al., 2013) The clinical significance of this finding is unclear. Although testosterone supplementation therapy has been shown to increase peak muscle strength and peak work load achieved in patients with COPD (not necessarily with testosterone deficiency) maximal oxygen uptake and health related quality of life were not improved. More data are awaited to determine whether screening patients with COPD for testosterone deficiency is clinically necessary and whether supplementation in deficient patients can induce any clinically relevant benefits.

### **O7.10 Cognitive impairment**

Cognitive dysfunction has been described in people with COPD as in other chronic diseases such as cardiac failure and diabetes. The frequency of cognitive dysfunction varies depending upon the battery of neuropsychological tests used, with the domains most influenced being memory and attention. In a meta-analysis of 655 patients with COPD and 394 control subjects, cognitive function was associated with severity of COPD only in those with severe to very severe disease (Schou et al., 2012). It is unclear how detected deficits in cognitive function relate to clinical disability in performing self-management and self-care, nor is it clear

which tests are most appropriate for assessing cognitive dysfunction in these patients. As memory and attention, as well as speed, co-ordination and learning ability were shown to be reduced, it may be important to consider level of cognitive impairment when assessing capacity for self-management, although this has not been clearly demonstrated.

## O7.11 Anaemia

Anaemia is a relatively uncommon comorbidity of COPD (Schnell et al., 2012, Barnes and Celli, 2009, Yohannes and Ershler, 2011, Almagro et al., 2012), either attributable to erythropoietin resistance (Markoulaki et al., 2011) or inflammation (Markoulaki et al., 2011, Rutten et al., 2013, Boutou et al., 2012), which may impair functional performance (Cote et al., 2007, Krishnan et al., 2006, Boutou et al., 2011) and health status (Krishnan et al., 2006, Boutou et al., 2011), contribute to worse survival (Haja Mydin et al., 2013, Kollert et al., 2013, Martinez-Rivera et al., 2012, Boutou et al., 2013, Cui et al., 2012, Chambellan et al., 2005), and be associated with increased health care utilization costs (Shorr et al., 2008, Halpern et al., 2006). Red cell transfusion appears to be a reasonable strategy for those with severe anaemia (Schonhofer et al., 1998), though there is no evidence of benefit from RCTs.

## O8. Hypoxaemia and pulmonary hypertension

Identify and treat hypoxaemia and pulmonary hypertension (Cranston et al., 2005) [evidence level I]

### Hypoxaemia

Hypoxaemia in COPD patients should be identified and corrected with long term oxygen therapy as this has been shown to improve survival and quality of life (Nocturnal Oxygen Therapy Trial Group, 1980), (Medical Research Council Working Party, 1981) (see O8.1). Hypoxaemia is best screened for using pulse oximetry, however should be confirmed using arterial blood gas (ABG) measurement. Use of ABGs also allows for the detection of hypercapnia which may complicate long term oxygen use. The indication for long term oxygen use are:

- Arterial PaO<sub>2</sub> less than or equal to 55mmHg or
- Arterial PaO<sub>2</sub> less than or equal to 59mmHg in the presence of pulmonary hypertension, right heart failure or polycythaemia

### Pulmonary Hypertension

The definition of pulmonary hypertension (PHT) was revised in 2009. PHT is now defined as a mean Pulmonary Artery Pressure (PAP) > 25mmHg at rest measured by right heart catheterization. (Simonneau et al., 2009) PAP assessed during exercise is no longer part of the definition. PHT was seen in approximately 50% of patients with severe emphysema (FEV<sub>1</sub> 27% of predicted) studied as part of the National Emphysema Treatment Trial (NETT) (Scharf et al., 2002) but only 5% of these patients had moderate to severe PHT (mean PAP > 35mmHg). In these patients, no correlation was found between PaO<sub>2</sub> and mean PAP although FEV<sub>1</sub>, Pulmonary Capillary Wedge Pressure and D<sub>L</sub>CO were correlated in a multiple regression model. In those COPD patients with severe PHT, hypoxaemia, reduced D<sub>L</sub>CO and PAP are often more impaired than would be expected for their degree of airflow obstruction. (Chaouat et al., 2005) There are several postulated mechanisms for PHT in COPD. (Chaouat et al., 2008) The presence of PHT is associated with a worse prognosis (Chaouat et al., 2008) and increased hospitalisation. (Kessler et al., 1999) This has resulted in several small studies of non selective and selective vasodilators.

No pharmacological therapies have shown to be effective to date. An early study of the non selective dihydropyridine calcium antagonist vasodilator felodipine in COPD showed improved haemodynamics. (Sajkov et al., 1993) However, the low efficacy and high adverse effect profile make such drugs an unattractive option. The first report of a selective pulmonary vasodilator, nitric oxide (NO) in stable COPD (Barbera et al., 1996) was disappointing in that hypoxia was exacerbated, presumably through the mechanism of worsening ventilation/perfusion (V/Q) mismatching. A subsequent 40 patient randomised trial assessed "pulsed" (a burst at the start of inspiration) NO and demonstrated that improved haemodynamics without exacerbation of hypoxia (Vonbank et al., 2003) was possible. No further randomised controlled trials of selective pulmonary vasodilators in COPD patients have yet been published. Although endothelin-1 receptor antagonists and other agents have been used to treat non-COPD-related PHT, a trial of bosentan in COPD (Stolz et al., 2008) once again induced adverse effects on gas exchange and quality of life. Similarly, two randomised controlled trials of the phosphodiesterase-5 inhibitor sildenafil failed to demonstrate improvements in cardiac output, 6MWT or maximal workload on cardiopulmonary exercise testing in COPD patients. (Holwerda et al., 2008, Rietema et al., 2008) Well designed trials of agents which selectively dilate the pulmonary vascular bed without worsening V/Q mismatching are urgently needed.

PHT and right heart failure may be complications of acute exacerbations of COPD. Therapy in these patients has generally been directed at reversing hypoxia and hypercapnoea with bronchodilators, corticosteroids, antibiotics as well as supplemental oxygen and ventilatory support. A 16 patient randomised placebo controlled trial of IV prostacycline showed no benefit, but exacerbated hypoxia in patients receiving conventional therapy including mechanical ventilation for an acute exacerbation of COPD (Archer et al., 1996)

Thus, there are no data at present that clearly support the use of vasodilators generally in COPD patients with PHT. However

severe PHT is uncommon in patients with even advanced emphysema. As such, where appropriate, a careful search for other potential causes of PHT should be undertaken and an alternative diagnosis considered.

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. A pulmonary artery to aorta ratio of greater than one as measured on CT chest has been used as a marker of possible pulmonary hypertension. Wells et al used this measure in over 1,000 subjects and prospectively found its presence lead to a significantly increased risk of future exacerbations odds ratio, 3.44; 95% CI, 2.78 to 4.25;  $P < 0.001$  (Wells et al., 2012) [evidence level III-2].

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-oesophageal 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. (Medical Research Council Working Party, 1981), (Nocturnal Oxygen Therapy Trial Group, 1980, Weitzenblum et al., 1985, Gorecka et al., 1997, Zielinski et al., 1998) (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). An Australian trial of hypoxaemic COPD patients with hypercapnia (n=144) randomised to long term oxygen therapy alone or with added non-invasive ventilation (NIV) found a small mortality benefit in the NIV group, at the expense of worse quality of life (McEvoy et al., 2009) [evidence level II]. A 2013 Cochrane meta-analysis comparing nocturnal NIV to standard care alone in patients with stable COPD and hypercapnia found no benefit. There was no significant change to gas exchange, exercise tolerance, quality of life, lung function, respiratory muscle strength or sleep efficiency. (Struik et al., 2013) The authors concluded that there is insufficient evidence to support widespread NIV use in stable COPD [evidence level I]. A systematic review comparing NIPPV to a range of other interventions including spontaneous breathing and sham ventilation, identified six RCTs and nine non-RCTs (Kolodziej et al., 2007). The RCTs found no significant improvement in outcomes for NIPPV. Arterial blood gases were no different; weighted mean difference for PaO<sub>2</sub> was 1.86mmHg (95% CI -0.60 to 4.32) and for PaCO<sub>2</sub> 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. Although preliminary studies have suggested that the addition of NIPPV to long-term therapy may have some beneficial effects on CO<sub>2</sub> retention and shortness of breath, based on a 12-month study (Casanova et al., 2000) and a 24-month study (Clini et al., 2002) in stable COPD patients with chronic respiratory failure, its widespread use cannot be advocated as yet. (Elliott, 2002) However, compared with long-term oxygen therapy alone, the addition of NIPPV has some beneficial effects on CO<sub>2</sub> retention and shortness of breath. (Clini et al., 2002)

**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. (NHLBI/WHO Workshop Report, April 2001) 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. (Barbera et al., 1996), (Jones and Evans, 1997) 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 (e.g., dihydropyridine calcium antagonists) have been shown to reduce right ventricular pressure with minimal adverse effects and increased well-being, at least in the short term (Sajkov et al., 1993), (Sajkov et al., 1997) Nitric oxide worsens V/Q mismatching and is therefore contraindicated in patients with COPD. (Barbera et al., 1996), (Jones and Evans, 1997)

## O9. Surgery

In selected patients, a surgical approach may be considered for symptom relief (Benditt and Albert, 1997, Mehran and Deslauriers, 1995, Cooper et al., 1995, Geddes et al., 2000, Fishman et al., 2003) [evidence level III-2]

None of the current surgical approaches in patients with COPD provides a survival advantage. (NHLBI/WHO Workshop Report, April 2001), (Benditt and Albert, 1997) 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. (Mehran and Deslauriers, 1995) Giant bullae can be defined as occupying more than 50% of the hemithorax with definite displacement of adjacent lung tissue. (Laros et al., 1986)

### O9.2 Lung volume reduction surgery

Lung volume reduction surgery (LVRS) involves resection of the most severely affected areas of emphysematous, non-bullous lung. (Cooper et al., 1995) This can improve lung elastic recoil and diaphragmatic function. (Geddes et al., 2000) 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. (NETT, 1999) 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. (Ries et al., 2005) There was no overall survival advantage of surgery, but after 24 months there was significant improvement in exercise capacity in the surgical group. Patients allocated to LVRS took significantly longer (median 2 v 1 year) than those who continued medical therapy to reach a composite endpoint of death or meaningful deterioration in disease related quality of life. (Benzo et al., 2009) 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 (Fishman et al., 2003) [evidence level II]. Longer term follow up from NETT has now been published. (Criner et al., 2011) In a subgroup of patients who underwent right heart catheterisation, there was no evidence for an increase in pulmonary artery pressures. Nonetheless, surgical lung volume reduction is now rarely performed either in the US or Australia. A variety of nonsurgical techniques are currently under investigation. These include endobronchial one-way valves, self-activating coils, targeted destruction of emphysematous tissue, bypass tract airway stenting and transpleural ventilation. Two randomised controlled trials examining Zephyr endobronchial valves have been reported (Sciurba et al., 2010, Herth et al., 2012). Both trials recruited highly selected COPD patients with severe obstruction and gas trapping and excluded patients with significant hypercapnia ( $\text{PaCO}_2 > 50\text{mmHg}$ ) and poor mobility ( $6\text{MWD} < 140\text{m}$ ). Patients underwent pulmonary rehabilitation prior to randomisation. Neither trial had a sham placebo procedure and the Herth trial used technically more advanced valves. Both trials reported very small improvements in FEV1 and quality of life. Data on improvement in 6MWD was conflicting. Data on adverse events were also conflicting with the Sciurba trial reporting high hospital admissions for COPD exacerbations. In summary, endobronchial valves may provide a small benefit to highly selective patients but should only be considered in specialised centres.

### 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. (Orens et al., 2006) 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 (Orens et al., 2006) 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
- $\text{FEV}_1 < 20\%$  and either  $\text{D}_t\text{CO} < 20\%$  or homogeneous emphysema (Fishman et al., 2003)

The experience of one Australian lung transplantation centre has been reviewed. (Gunes et al., 2006) 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  $\alpha$ 1 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](http://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 (Dean, 2008). 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 (Claessens et al., 2000)
- COPD patients were more likely to die in hospital (Gore et al., 2000)
- COPD patients were less likely to receive palliative support (Gore et al., 2000)

The Gold standards framework suggests three triggers for supportive or palliative care (Gold Standards Framework Programme, 2005):

- 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 (Jennings et al., 2002) [evidence level I]. Opioids have a small but statistically significant benefit in reducing dyspnoea [evidence level I]. In one study, the most significant adverse effect was constipation and there was no significant increase in respiratory depression, sedation or nausea and vomiting (Abernethy et al., 2003). Nonetheless, opioids should be used with care in COPD. There is little evidence to support nebulised opioids in the treatment of breathlessness (Jennings et al., 2002). 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 be.g.in 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. from the Office of the Public Advocate in Victoria: <http://www.publicadvocate.vic.gov.au/>, but these are also available through any solicitor or le.g.al service and may vary between States and Territories 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 le.g.al 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 be.g.in the discussion and not leave it too late in the patient's disease course.

A useful resource to guide patients in making these choices is [www.respectingpatientchoices.org.au/](http://www.respectingpatientchoices.org.au/)

### **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(Abernethy et al., 2010) [evidence level II]. The prescription of oxygen in these clinical situations should be made on an individual basis. 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. A systematic review of 47 studies with an average follow-up of 11 years found a significantly higher decline in FEV<sub>1</sub> in people who continued to smoke compared to those who ceased (Lee and Fry, 2010) [evidence level I]. The annual decline in FEV<sub>1</sub> for those who stopped at the beginning of follow-up was 12.4 ml/yr (95%CI 10.1 to 14.7) and for those who stopped during the period of follow-up 8.5 ml/yr (95% CI 5.6 to 11.4), both less than people who continued to smoke. While there were limitations to the data, the review clearly found that in people who continue to smoke the annual decline in FEV<sub>1</sub> is >10 ml/yr greater than in people who have never smoked or stopped smoking. Reduction of exposure to occupational dust, fumes and gases and to indoor and outdoor air pollutants is also recommended. (NHLBI/WHO Workshop Report, April 2001) Influenza immunisation 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 (Fletcher and Peto, 1977), (Tashkin et al., 1996), (Anthonisen et al., 2002) [evidence level I]

The Lung Health Study (LHS) was a North American multicentre three-arm randomized controlled trial of an intensive smoking cessation intervention with or without inhaled ipratropium or placebo compared with usual care in smokers recruited from the community with mild to moderate airflow obstruction. Longitudinal data from the LHS were used to explore the association between spirometric measures and the annual decline in FEV<sub>1</sub> over five years and mortality at 12 years. (Drummond et al., 2012) At baseline, the cohort (n = 5,885), predominantly Caucasian, had a mean age of 49 +/- 6.8 years, and all were active smokers with average smoking history of 41 +/- 19 pack years. Mean FEV<sub>1</sub>/FVC were 0.63 +/- 0.06 (pre BD) ; and 0.65 +/- 0.06 (post BD). 21% had a post-bronchodilator FEV<sub>1</sub>/FVC greater than or equal to 0.7. At 5-year follow-up, 147 (2.5%) of the cohort had died, while 575 (9.8%) had died at 12 to 15 years. The unadjusted annual decline in absolute FEV<sub>1</sub> for the entire cohort was 53.1 +/- 0.6 ml at year 5 and 53.9 +/- 0.5 ml at year 12. When the study cohort was stratified by smoking pattern (sustained quitter, intermittent quitter, or continuous smoker), an association between lower baseline lung function and accelerated decline in lung function was observed in all groups, except sustained quitters. Excessive lung function decline occurred at FEV<sub>1</sub>/FVC of 0.65 or below (HR 1.36; 95% CI - 1.08-1.72; p = 0.01) and the risk of death increased at FEV<sub>1</sub>/FVC of 0.55 or below (HR 1.31; 95% CI - 1.01-1.70; p = 0.04).

A comprehensive review of smoking cessation in patients with respiratory diseases has been published by the European Respiratory Society (<http://erj.ersjournals.com/content/29/2/390.long>) (Tonnesen et al., 2007) A successful tobacco control strategy involves integration of public policy, information dissemination programs and health education through the media and schools. (NHLBI/WHO Workshop Report, April 2001) Smoking prevention and cessation programs should be implemented and be made readily available (NHLBI/WHO Workshop Report, April 2001), (World Health Organization, 1999) [evidence level I]. Pharmacotherapies double the success of quit attempts. Behavioural techniques further increase the quit rate. (US Public Health Service, 2000), (Peters and Morgan, 2002), (Wilson et al., 1990), (Britton and Knox, 1999), (Kottke et al., 1988), (Baillie et al., 1994), (van der Meer et al., 2003) [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. (US Public Health Service, 2000), (Peters and Morgan, 2002)

Smoking cessation has been shown to be effective in both sexes, in all racial and ethnic groups tested, in pregnant women (NHLBI/WHO Workshop Report, April 2001) and people with COPD. (van der Meer et al., 2003) There is good evidence that smoking cessation strategies in people with COPD are cost-effective, both for counselling and pharmacotherapy, with low costs per quality-adjusted life years gained. (Hoogendoorn et al., 2010b) A small body of evidence suggests that counselling combined with nicotine replacement therapy is more effective than other combinations and single smoking cessation treatments in COPD, with an odds ratio compared to usual care alone of 5.08. (Strassmann et al., 2009) A range of health professionals can help smokers quit (Lancaster and Stead, 2004), (Rice and Stead, 2004), (Tonnesen et al., 2006), 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.([NHLBI/WHO Workshop Report, April 2001](#)) Personalising smoking cessation advice based on lung function results increase cessation rates.([Parkes et al., 2008](#)) Currently accepted best practice is summarised in the 5-A strate.g.y:([NHLBI/WHO Workshop Report, April 2001](#))

- Ask and identify smokers
- Advise smokers about the risks of smoking and benefits of quitting and discuss options
- Assess the degree of nicotine dependence and motivation or readiness to quit
- Assist cessation — this may include specific advice about pharmacological interventions or referral to a formal cessation program if available
- Arrange 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 *maintaining abstinence* (*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([Lancaster et al., 2000](#))[evidence level I]

Pharmacotherapies for nicotine dependence are effective and should be added to counselling if necessary and in the absence of contraindications ([NHLBI/WHO Workshop Report, April 2001](#)) [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.([NHLBI/WHO Workshop Report, April 2001](#)) 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. ([Stead et al., 2008](#)) 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.([Schwartz, 1987](#))

NRT is safe in patients with stable cardiac disease such as angina pectoris(Joseph et al., 1996, Mahmarian et al., 1997, Nitenberg and Antony, 1999) [evidence level II], and acute coronary syndromes ([Meine et al., 2005](#)) [evidence level III-2]. 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 adverse 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 adverse 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. (Hughes et al., 2007) 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 antimuscarinic 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  $\geq 6$  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], (NHLBI/WHO Workshop Report, April 2001) 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  $\alpha 4\beta 2$  nAnti-Cholinergic Receptors ( $\alpha 4\beta 2$  nAChR), which stimulate the release of dopamine. (Coe et al., 2005) 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. (Cahill et al., 2008) 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. Efficacy has also been demonstrated in people with COPD in a double-blind, multinational study of 504 patients with mild to moderate COPD. (Tashkin et al., 2011a) The primary end point of carbon monoxide-confirmed continuous abstinence rate (CAR) for weeks 9 to 12 was significantly higher for patients in the varenicline group (42.3%) than for those in the placebo group (8.8%) (OR, 8.40; 95% CI, 5-14;  $P < .0001$ ) [evidence level II]. 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.

(<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106540.htm>). Concerns were also raised over adverse cardiovascular events associated with the drug in a systematic review by Singh (Singh et al., 2011), subsequently re-examined to address perceived weaknesses of the first study (Prochaska and Hilton, 2012), which included the exclusion of trials with no events, the inclusion of adverse events well beyond the treatment period and use of the Peto odds ratio for rare events. The re-examination included over 8,000 participants from 22 studies, and found a rate for serious cardiovascular events of 0.63% for varenicline and 0.47% for placebo, which were not significantly different (risk difference = 0.27%, 95% confidence interval, -0.10 to 0.63). 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). An 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. (Aubin et al., 2008)

#### **P1.2.4 Cannabinoid type 1 receptor antagonists**

Central cannabinoid (CB1) receptors have 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. (Pomerleau et al., 2000) A Cochrane systematic review has assessed the effect of rimonabant compared to placebo in aiding smoking cessation. (Cahill and Ussher, 2007) 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. (Gourlay et al., 2004) 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. (Hughes et al., 2000)

#### **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. Immunisations

### P2.1 Influenza immunisation

Influenza immunisation reduces the risk of exacerbations, hospitalisation and death (Nichol et al., 1994), (Poole et al., 2006) [evidence level I]

Annual influenza immunisation reduces by about 50% the development of severe respiratory complications and hospitalisation or death from both respiratory disease and all causes (Nichol et al., 1994), (Poole et al., 2006) [evidence level I]. The vaccine used in Australia does not contain a live virus and cannot cause an infection. Adverse 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. (Nichol et al., 1994), (Poole et al., 2006) A second immunisation in winter increases antibody levels. (NHLBI/WHO Workshop Report, April 2001)

### P2.2 Pneumococcal immunisation

Pneumococcal immunisation is known to be highly effective in preventing invasive bacteraemic pneumococcal pneumonia, but may be less effective in elderly or immunosuppressed patients. (Simberkoff et al., 1986) There is no direct evidence of its efficacy in preventing pneumococcal exacerbations of COPD (Walters et al., 2011a) [evidence level I], but prevention of pneumonia in these patients with already reduced respiratory reserve is a worthy goal in its own right. (Simberkoff et al., 1986, Williams and Moser, 1986, Davis et al., 1987) so pneumococcal immunisation (polyvalent covering 23 virulent serotypes) is recommended in this group [evidence level II]. (NHLBI/WHO Workshop Report, April 2001) There is no evidence or rationale for immunising more frequently in COPD. Please see the link to The Australian Immunisation Handbook on the NHMRC's website for further details: <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-pneumococcal>

The additive effect of pneumococcal immunisation to annual influenza immunisation has been studied in a randomised, controlled trial over two years in Japanese patients with chronic lung disease. (Furumoto et al., 2008) They found a significant additive effect of receiving both vaccines on exacerbations in patients with COPD (influenza vaccine alone = 26% vs. both vaccines = 10.3%,  $p = 0.037$ ), supporting current recommendations for dual immunisation.

### P2.3 Haemophilus influenzae immunisation

Six randomised trials of oral monobacterial whole cell killed non-typable haemophilus influenzae vaccine (Foxwell et al., 2003) found a significant reduction in the incidence of bronchitic episodes three months after immunisation, 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 [evidence level I]. A placebo controlled RCT (Tandon et al., 2010) of an oral inactivated non-typable H. influenzae vaccine (HI-1640V) in 38 patients with severe COPD found a reduction in moderate to severe exacerbations, shorter duration of episodes, fewer prescriptions of antibiotics and reduced hospital admissions [evidence level II]. However, this vaccine is not currently available in Australia or New Zealand.

## P3. Immuno-modulatory agents

The available evidence suggests that the putative immuno-modulatory agent OM-85 BV is well tolerated (Sprenkle et al., 2004) [evidence level I]. However, consistent results across important clinical outcomes, such as exacerbation and hospitalisation rates, are lacking to determine whether it is effective. Further randomised, controlled trials enrolling large numbers of persons with well-defined COPD are necessary to confirm the effectiveness of this agent.

## P4. Antibiotics

Current evidence does not support long-term antibiotic use to prevent exacerbations in patients with COPD (Isada CM and Stoller JK, 1994), (Siafakas NM and Bouros D, 1998) [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. (Black et al., 2003) A 12

month randomised controlled trial of erythromycin 250mg bd in patients with moderate COPD found a significantly reduced risk of exacerbation with a rate ratio of 0.65 (95%CI 0.49-0.86) (Seemungal et al., 2008) [evidence level II].

A 12 month randomised controlled trial of azithromycin 250 mg daily vs. placebo was undertaken in patients with COPD who were using supplemental oxygen, or had received a course of systemic corticosteroids for respiratory problems in the past year, or had visited an Emergency Department for a COPD exacerbation within the past year, or had been hospitalised for a COPD exacerbation within the past year (Albert et al., 2011) The study found that azithromycin significantly increased the median time to the first exacerbation, reduced exacerbation rates, and improved quality of life in some patients [evidence level II]. However, hearing loss was more common in a small proportion of patients, and more macrolide-resistant organisms were seen. Patients had been excluded from the study if they had resting tachycardia, prolonged corrected QT interval or use of medications that could prolong this, or hearing impairment. It should be noted that azithromycin is not available on the PBS for long term use.

## P5. Long-acting bronchodilators

### P5.1 Anticholinergics (Antimuscarinics)

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 (Barr et al., 2005) [evidence level I]. Another systematic review of 22 trials with 15,276 participants found that anticholinergic (antimuscarinic) 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 antimuscarinic agents to prevent one death (Salpeter et al., 2006) [evidence level I].

A randomised double blind placebo controlled trial of four years duration found that tiotropium was associated with a reduced risk of death at end of treatment (Hazard Ratio 0.84, 95% CI 0.73-0.97). (Celli et al., 2009) It would be necessary to treat at least 53 patients to prevent one death. The precise statistical significance varied with the period of analysis. The hazard ratio for tiotropium compared to placebo varied from 0.87 (95%CI 0.76-0.99, p=0.034) for the full 4 years to 0.89 (0.79-1.02, p=0.086) for 4 years+ 30 days [evidence level II]. A pre-specified subgroup analysis of this four year trial (Decramer et al., 2009) found that tiotropium reduced the rate of decline of post-bronchodilator FEV<sub>1</sub> in patients with GOLD II COPD (43mls/year versus 49ml/year, p=0.024). However, the of pre-bronchodilator FEV<sub>1</sub> decline was not different between the groups.

### P5.2 Comparison of Inhaled Medications

A systematic review examined the relative effectiveness of inhaled medications to reduce the risk of exacerbations of COPD (Puhan et al 2009). The authors identified 35 randomised controlled trials of at least 4 weeks duration that enrolled 26,786 patients with COPD of whom 27% had one or more exacerbations. All regimens significantly reduced the odds of exacerbation compared with placebo - no single inhaled medication was more effective than another. If FEV<sub>1</sub> was ≤ 40% predicted, long acting antimuscarinics, inhaled corticosteroids and combination treatment reduced exacerbations significantly compared with long-acting beta agonists alone. However the authors did not have FEV<sub>1</sub> data for individual patients.

In 2012, Chong et al (Chong et al., 2012) performed a meta-analysis that compared tiotropium to a range a long acting beta-agonists, data from over 11,000 patients were included and trials were at least 3 months long. Chong reported that tiotropium was more effective in preventing COPD exacerbations leading to hospitalisation (odds ratio 0.86; 95% CI 0.79 to 0.93). There was no difference in mortality, all-cause hospitalisations, quality of life and lung function. There were fewer serious adverse events with tiotropium (OR 0.88; 95% CI 0.78 to 0.99).

## P6. Corticosteroids

The effect of inhaled corticosteroids on the disease progression in COPD has been the subject of a series of controlled trials and systematic reviews and the effect remains unclear. A Cochrane systematic review found benefits of inhaled corticosteroids in reducing exacerbations and reducing decline in quality of life, but no consistent benefit on rate of decline in lung function or mortality (Yang et al., 2012) [evidence level I]; see Section **O3.2 Inhaled corticosteroids** for details). While these data do not support the use of inhaled corticosteroids in all people with COPD, they are indicated for those with more severe disease (FEV<sub>1</sub> <50% predicted) and a history of frequent exacerbations.

## P7. Mucolytic agents

Mucolytics may reduce the frequency and duration of exacerbations(Poole and Black, 2010) [evidence level II]

Mucolytics, including N-acetylcysteine (NAC), ambroxol (3), sobrerol, carbocysteine, sobrerol, letosteine, cithiolone, iodinated glycerol, N-isobutyrylcysteine (NIC), myrtol and erdoesteine have multiple possible actions in COPD including decreasing sputum viscosity, and antioxidant, anti-inflammatory or antibacterial activity. A 2010 Cochrane review(Poole and Black, 2010) included 9 studies in COPD and 19 studies in chronic bronchitis. The authors found treatment with mucolytics was associated with a small reduction in acute exacerbations, WMD -0.04 per month (95% CI -0.05 to -0.03) 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 corticosteroids are not prescribed. The caveat on the use of inhaled corticosteroids 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 trial of 709 subjects with COPD randomised to carbocysteine or placebo(Zheng et al., 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 corticosteroids was only 15% in the placebo and 18% in the carbocysteine arms(Zheng et al., 2008) [evidence level II]. A placebo controlled trial of N-acetylcysteine in patients with stable COPD found significant improvement in small airway function and reduction in the frequency of exacerbations (Tse et al., 2013) [evidence level II].

## P8. Humidification therapy

A study by Rea et al(Rea et al., 2010) found that high flow humidified air delivered via nasal cannulae for up to 2 hours daily reduced annual exacerbation days and days to first exacerbation but not exacerbation frequency compared with usual care in a group of 108 patients, with COPD/bronchiectasis. Quality of life and lung function also improved. No sham treatment was given. No cost evaluation data were provided in this study.

## P9. 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.(NHLBI/WHO Workshop Report, April 2001) Please see comments in section D. A prospective trial in the primary care setting(Abramson et al., 2010) randomised patients who had been prescribed inhaled medication to a) three monthly review and spirometry, b) usual care and spirometry before and after trial and c) usual care. This study did not show any significant improvement in quality of life or other health outcomes. Possible explanations for the negative results include limited power, few events and inclusion of doctor diagnosed obstructive lung disease as opposed to spirometry defined patients. Spirometry remains the gold standard for establishing the diagnosis of COPD.

## P10. Oxygen therapy

Long-term oxygen therapy (>15 h/day)

prolongs life in hypoxaemic patients ( $\text{PaO}_2 < 55 \text{ mmHg}$ , or  $7.3 \text{ kPa}$ ) (Medical Research Council Working Party, 1981),(Nocturnal Oxygen Therapy Trial Group, 1980),(Weitzenblum et al., 1985, Gorecka et al., 1997, Zielinski et al., 1998),(American Thoracic Society, 1995),(Siafakas et al., 1995, Tarcy and Celli, 1995) [evidence level I]

Long term oxygen therapy reduces mortality in COPD.(Medical Research Council Working Party, 1981),(Nocturnal Oxygen Therapy Trial Group, 1980),(Gorecka et al., 1997, Zielinski et al., 1998),(American Thoracic Society, 1995),(Siafakas et al., 1995, Tarcy and Celli, 1995) It may also have a beneficial impact on haemodynamics, haematological status, exercise capacity, lung mechanics and mental state.(Weitzenblum et al., 1985),(Zielinski et al., 1998),(Tarcy and Celli, 1995) 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  $\text{PaO}_2$  consistently  $< 55 \text{ mmHg}$  ( $7.3 \text{ kPa}$ ;  $\text{SpO}_2 88\%$ )(Medical Research Council Working Party, 1981),(Nocturnal Oxygen Therapy Trial Group, 1980)when breathing air, at rest and awake [evidence level I]. If oxygen is prescribed when the patient's condition is unstable (e.g., 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 PaO<sub>2</sub> is 55–59 mmHg (7.3–7.9 kPa; SpO<sub>2</sub> < 90%). (Siafakas et al., 1995), (American Thoracic Society, 1995) Continuous oxygen therapy is of most benefit for patients with increased arterial PaCO<sub>2</sub> (> 45 mmHg, or 6 kPa). (Nocturnal Oxygen Therapy Trial Group, 1980)

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. (Serginson et al., 2009)

**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. (Ram and Wedzicha, 2002) However, use of intermittent oxygen therapy may be considered for:

- People who experience oxygen desaturation on exertion. (Ram and Wedzicha, 2002) 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. (Bradley and O'Neill, 2005) 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, oxygen saturation and dyspnoea severity on a walking test (e.g. six-minute walk test [6MWT], incremental shuttle walk test [ISWT], endurance shuttle walk test [ESWT] or treadmill test) when breathing oxygen and when breathing room air. It is important to consider that most patients will walk further on a repeat test. Therefore, when assessing the impact supplemental oxygen has on functional exercise capacity, it is important that the patient has completed a practise walk test and that the best 6MWD is used to determine response (Chandra et al., 2012). Without a practise test, the effect of test repetition (i.e. the learning effect) could be mistaken for an increase in exercise capacity due to supplemental oxygen. Most of the learning effect for the 6MWT and ISWT occurs between the first and second tests with little further improvement on a third test. (Eiser et al., 2003) Studies of large numbers of patients with COPD have shown that over 80% of patients walk further on a second 6MWT performed on the same day (n=245; mean, 95% CI increase of 37m, (33, 41m) (Jenkins, 2011) or on consecutive days (n=1,514; mean increase 27m (-37, 107m). (Hernandes et al., 2011) A learning effect has also been demonstrated for the externally paced ISWT with patients walking 24m (standard deviation 47m) further on a second test (n=392). (Dyer et al., 2011) The ESWT requires prior performance of the ISWT in order to derive the workload (i.e. walking speed) for the ESWT. It would appear that a practice ESWT may not be necessary providing patients have previously performed two ISWTs. (Revill et al., 2009, McKeough et al., 2011) Nevertheless, for any given individual, the distance walked during these tests varies both within and between days. (Bansal et al., 2008) (Dolmage et al., 2011) and therefore the prescription of supplemental oxygen should not be based solely on an improvement in the distance achieved on a walking test. Factors such as a reduction in dyspnoea and agreement to use oxygen in the home setting should also be considered. 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. (Turner et al., 2004), (Cockcroft et al., 1985), (Poulain et al., 2003) 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. (Nonoyama et al., 2007) 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 (Bradley et al., 2007);
- Breathless patients, including those who desaturate on exercise, who are not shown to be hypoxic at rest do not benefit in terms of dyspnoea, quality of life and function from ambulatory oxygen therapy (Moore et al., 2011) [evidence level II];
- 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 (O'Neill et al., 2006) [evidence level I] (O'Driscoll, 2008).

**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.

### **P10.1 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 PaO<sub>2</sub> 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 (e.g., cardiac impairment, anaemia). Exertion during flight will exacerbate hypoxaemia.

The American Thoracic Society currently recommends that PaO<sub>2</sub> during air travel should be maintained at more than 50 mmHg (6.7 kPa). At altitude, PaO<sub>2</sub> can be estimated from PaO<sub>2</sub> at sea level by means of published nomograms. If the PaO<sub>2</sub> at sea level is less than 70 mmHg (9.3 kPa), PaO<sub>2</sub> at 2300 metres is less than 50 mmHg (6.7 kPa). The natural conclusion is that all patients with a PaO<sub>2</sub> less than 70 mmHg (9.3 kPa) at rest at ground level should receive supplemental oxygen. (American Thoracic Society, 1995, Ahmedzai et al., 2011)

Many lung function laboratories perform high altitude simulation tests (HAST) to assess fitness to fly. These measure arterial blood gas levels or transcutaneous oxygen saturation while breathing a mixture of 15% oxygen and 85% nitrogen, mimicking conditions at 2800 metres. A study suggested that if a portable oxygen concentrator was used, a pulse setting of >2 litres was likely to be necessary in order to achieve SpO<sub>2</sub> ≥ 90% in most patients requiring oxygen during flight. (Akerø et al., 2011)

### **P11 Alpha1-antitrypsin deficiency**

A systematic review of two small randomised controlled trials concluded that there was lack of evidence of clinical benefit from alpha-1 antitrypsin augmentation therapy (Gotzsche and Johansen, 2010) [evidence level I]. Alpha-1 antitrypsin augmentation therapy is not routinely available in Australia.

## ***D: Develop support network and self-management***

COPD imposes handicaps which affect both patients and carers(Celli, 1995, Fishman, 1994),(Spruit et al., 2013) (Morgan et al., 2001) [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.(Mathers et al., 1999) Depression, anxiety, panic disorder, and social isolation add to the burden of disease as complications and comorbidities accumulate. Patients with severe COPD often have neuropsychological deficits suggestive of cerebral dysfunction. The deficits are with verbal(Incalzi et al., 1997) and visual short-term memory(Crews et al., 2001), simple motor skills(Roehrs et al., 1995), visuomotor speed and abstract thought processing(Grant et al., 1982). Severe COPD is also associated with lower cognitive performance over time (Hung et al., 2009) [evidence level III-2].

People with chronic conditions are often 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(Jones and Peters, 1992) 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(Wagner et al., 1996). 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)(Adams et al., 2007). 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(Peytremann-Bridevaux et al., 2008) assessed the impact of COPD management programs attended by patients, which they defined as interventions with two or more different components (e.g. physical exercise, self-management, structured follow-up), at least one of which continued for 12 months, were delivered by two or more health care professionals and incorporated patient education. It found such programs improved exercise capacity and health related quality of life, and reduced hospitalisation [evidence level I]. However, it is unclear from this review which specific components of the disease management programs contribute the most benefit to patients. A Cochrane Review(Kruijs et al., 2013) examined 26 trials of integrated disease management programs defined as "a group of coherent interventions designed to prevent or manage one or more chronic conditions using a systematic, multidisciplinary approach and potentially employing multiple treatment modalities." The review found positive effects on disease-specific QoL measured by the Chronic Respiratory Questionnaire (all domains) and on the impact domain of the St George Respiratory Questionnaire. There were also positive effects on exercise tolerance, hospital admissions and hospital days per person [evidence level I].

In a similar approach, a large multicentre randomised controlled trial(Rice et al., 2010) involving veterans who received a single education session, an action plan for self-treatment of exacerbations and monthly follow-up calls from a case manager, found that, when compared to usual care, the intervention group had a significant reduction in hospitalisation and ED visits for COPD, mortality and quality of life, measured with the Chronic Respiratory Questionnaire [evidence level II]. An alternative approach of home care outreach nursing was studied in a systematic review by Wong(Wong et al., 2012), in which the intervention included home visits to provide education and social support, identify exacerbations and reinforce correct inhaler technique. They also found a significant benefit in quality of life, measured by the St George’s Respiratory Questionnaire, but no significant effect on mortality or hospitalisations [evidence level I]. In all these studies, it remains unclear which specific components contribute the most benefit to patients, are the most cost effective or should be combined to provide optimal benefit on the many different outcomes. Telehealthcare in COPD is the most recent of these types of interventions to be taken up. It appears it may have an impact on quality of life and emergency attendances in COPD, however, further research is needed to clarify its precise roles, as to date trials have included telecare as part of more complex packages (McLean et al., 2011)[evidence level I]. A 2011 systematic review of telemonitoring in the absence of other care packages determined that the benefit is not yet proven and that further work is required before wide-scale implementation of telemonitoring should be supported.(Bolton et al., 2011)

### Box 7: Comparison of outcomes for COPD management programs

Study/Outcome	Mortality	Hospitalisation	QOL	Exercise
Peytremann-Bridevaux	OR = 0.85 (0.54 to 1.36)	Benefit in 7/10 studies	Not reported	WMD = 32.2 (4.1 to 60.3)
Rice	#MD = 3.7 (-1.4 to 8.8)	*MD = 0.34 (0.15 to 0.52)	MD = 5.1 (2.5 to 7.6)	Not reported
Wong	OR = 0.72 (0.45 to 1.15)	OR = 1.01 (0.71 to 1.44)	WMD = -2.60 (-4.81 to -0.39)	WMD = 5.05 (-15.08 to 25.18)
McLean	OR = 1.05 (0.63 to 1.75)	OR = 0.46 (0.33 to 0.65)	WMD = -6.57 (-13.62 to 0.48)	Not reported

Outcome presented as OR = odds ratio or (W)MD = (weighted) mean difference, with 95% confidence intervals in brackets.  
\*Hospitalisation and ED visits. # difference per 100 patient years.

## D1. Support team

Enhancing quality of life and reducing handicap requires a support team (American Thoracic Society, 1995)

Patients and their family/friends should be actively involved in a therapeutic partnership with a range of health professionals (Celli, 1995), (Spruit et al., 2013), (Ries et al., 1995, Lorig et al., 1999) [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 6).

**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 Other specialist physicians

COPD is an important co-morbidity in older people which impacts on comprehensive medical management and quality of life. It is important to note that the support team involved in the management of COPD patients may include a geriatrician, cardiologist, endocrinologist and psychiatrist amongst others.

### **D1.3 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 (e.g., medications and response to worsening of symptoms);
- organisation of multidisciplinary case conferences and participation in care-plan development; and
- assessment of the home environment.

### **D1.4 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 (e.g., after LVRS), and assessment and treatment of musculoskeletal disorders commonly associated with COPD.

### **D1.5 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.

### **D1.6 Social worker**

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

### **D1.7 Clinical psychologist/psychiatrist**

Anxiety and depression are common disorders in patients with COPD (Di Marco et al., 2006, Gudmundsson et al., 2006, Kunik et al., 2005, Laurin et al., 2007, Schane et al., 2008), which worsen quality of life and add to disability (Gudmundsson et al., 2005, Ng et al., 2007, Xu et al., 2008, Laurin et al., 2009, Giardino et al., 2010, Eisner et al., 2010b). The prevalence of panic attacks and panic disorder in COPD are particularly high (Yellowlees et al., 1987, Pollack et al., 1996, Kunik et al., 2005, Laurin et al., 2007). There is promising evidence that anxiety and depression can be treated by clinical psychologists and psychiatrists using approaches such as cognitive behaviour therapy (Kunik et al., 2001, de Godoy and de Godoy, 2003, Livermore et al., 2010, Hynninen et al., 2010) [evidence level II]. Psychiatrists can also advise whether pharmacological treatment may be appropriate.

### **D1.8 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.

### **D1.9 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 (e.g., individual dosing dispensers) (Beney et al., 2000). 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.

### **D1.10 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, CO<sub>2</sub> retention and cor pulmonale. Dietitians play a central role in managing these problems.

### D1.11 Exercise physiologist

Exercise physiologists are predominantly involved in exercise testing, exercise prescription and supervision of exercise rehabilitative programs. They also provide patient education on the importance of regular exercise and on activity/behavioural modification. They may also play a role in the assessment of exertional oxygen and the exercise rehabilitation of associated comorbidities.

### D1.12 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 (e.g., 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 (Lorig et al., 1999) [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://lungfoundation.com.au/health-professionals/clinical-resources/copd/copd-action-plan/> 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/mbsprimarycareitems>.

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 (Effing et al., 2007, Trappenburg et al., 2011) [evidence level II]

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 is on delivering training for self-management skills to individuals through a range of interventions. (Osborne et al., 2008)

Patients with chronic illness who participate in self-management have better outcomes, including reduced healthcare costs, than those who do not. (Lorig et al., 1999) This study included some people with COPD. Studies of self-management support in COPD have shown mixed results. Some studies have found reductions in hospital and emergency department attendances (Bourbeau et al., 2003) (Rice et al., 2010) A Cochrane Review (Zwerink et al., 2014) of trials published between 1995 and August 2011 found a benefit for self-management interventions on health related quality of life and lower probability of respiratory-related hospitalisation but there was no effect on all-cause hospitalisation or mortality. This review does not include more recent studies while others have shown no benefit. (Bucknall et al., 2012), (Bischoff et al., 2012) One study found excess mortality in the self-management group. (Fan et al., 2012) The differences may be related to differences in the study populations, study context and extent of self-management support provided. In COPD, behavioural education alone is effective, although less effective than integrated pulmonary rehabilitation programs that include an exercise component. (Ries et al., 1995)

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 Walters et al (Walters et al., 2010) found that the use of action plans results in an increased ability to recognise and react appropriately to an exacerbation by individuals. However this review found that there was no reduction in healthcare resources utilisation or improved health-related quality of life. A 2011 randomised controlled trial showed that an individualised action plan, including ongoing support by a case manager, decreased the impact of exacerbations on health status. Action plans can be considered a key component of self-management programs in patients with COPD (Trappenburg et al., 2011) [evidence level II]. However, there is 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 corticosteroids 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 corticosteroids 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://lungfoundation.com.au/health-professionals/clinical-resources/copd/copd-action-plan/>)

## D4. Treat anxiety and depression

Anxious and depressive symptoms and disorders are common comorbidities in people with COPD (Yellowlees et al., 1987, Kunik et al., 2005, Ng et al., 2007, Xu et al., 2008, Eisner et al., 2010b) and have a range of negative impacts [evidence level I]

Anxiety symptoms in COPD are associated with worse quality of life (Giardino et al., 2010), self-management (Dowson et al., 2004) and exercise performance (Eisner et al., 2010b), and with increased medical symptom reporting (Katon et al., 2007), exacerbations (Laurin et al., 2012), hospitalisations (Yellowlees et al., 1987, Gudmundsson et al., 2005, Livermore et al., 2010), length of hospitalisations (Xu et al., 2008), medical costs (Katon et al., 2007, Livermore et al., 2010), and mortality (Celli et al., 2008). The prevalence of one anxiety disorder in particular, panic disorder, is approximately 10 times greater in COPD than the population prevalence of 1.5 – 3.5%, and panic attacks are commonly experienced (American Psychiatric Association, 2004, Smoller et al., 1996). Cognitive behaviour therapy has been shown to be an effective treatment for panic disorder in the physically healthy (Mitte, 2005) [evidence level I]. There is promising evidence from a number of small randomised controlled trials that cognitive behaviour therapy can treat anxiety symptoms in COPD (de Godoy and de Godoy, 2003, Hynninen et al., 2010, Livermore et al., 2010), and prevent the development of panic attacks and panic disorders (Livermore et al., 2010). Despite the common use of benzodiazepines in clinical practice, there is a lack of published evidence on their safety and effectiveness for treating anxiety in COPD. Caution is warranted in using these medications, due to their potential depressive effects on respiratory drive (Shanmugam et al., 2007), and their inherent risks in the elderly of dependence, cognitive impairment, and falls (Uchida et al., 2009). SSRI's (such as sertraline) have been recommended as better first line pharmacological therapies for anxiety in COPD. Psychiatrists can advise on the most appropriate medications for particular patients (Shanmugam et al., 2007).

People with COPD are not only at high risk of depressive symptoms and mood disorders, but are at higher risk than people with other chronic conditions (Ng et al., 2007, Omachi et al., 2009). When depressive symptoms are comorbid with COPD they are associated with worse health related quality of life (Ng et al., 2007, Omachi et al., 2009, Hanania et al., 2011) and difficulty with smoking cessation (Ng et al., 2007), and with increased exacerbations (Laurin et al., 2012), hospitalisations (Bula et al., 2001, Xu et al., 2008, Hanania et al., 2011), length of hospitalisations (Ng et al., 2007), medical

costs(Bula et al., 2001), and mortality(Bula et al., 2001, Ng et al., 2007). Depression may also influence decisions about end of life issues(Stapleton et al., 2005). As is the case for anxiety symptoms in COPD, there is evidence from small, randomised controlled trials that depressive symptoms can be decreased by cognitive behaviour therapy(de Godoy and de Godoy, 2003, Hynninen et al., 2010). Evidence for the effectiveness of particular antidepressant medications for mood disorders in COPD is still limited, with a few small, randomised controlled trials conducted(Argyropoulou et al., 1993, Lacasse et al., 2004, Eiser et al., 2005). Treatment with antidepressants can be complicated by poor tolerance of side effects such as sedation, which may cause respiratory depression(Evans et al., 1997). As with anxiety symptoms, psychiatrists can advise on which pharmacological treatments may be most appropriate for patients.

Larger randomised controlled trials evaluating the effectiveness of both psychological and pharmacological therapies for psychiatric disorders in COPD are clearly required(Baraniak and Sheffield, 2011)[evidence level I]. However, the existing evidence still warrants the referral of anxious and depressed people with COPD to clinical psychologists and psychiatrists for assessment and treatment. Depressed COPD patients referred to mental health specialists have lower odds of two year mortality than those treated in primary care settings(Jordan et al., 2009). Screening for clinically significant anxiety and depression, given their serious impacts, should therefore be part of routine care. The Hospital Anxiety Depression Scale is an example of an easily administered, widely used screening questionnaire, developed for use with medical patients(Zigmond and Snaith, 1983), and utilised in numerous studies of people with COPD(Gudmundsson et al., 2005, Ng et al., 2007, Xu et al., 2008, Livermore et al., 2010, Eisner et al., 2010b).

## D5. Referral to a support group

Greater improvements in exercise performance and self-efficacy for exercise have been shown for people with COPD who received education and psychosocial support than for those who received education without support(Ries et al., 1995). Patient support groups aim to empower participants to take a more active role in the management of their healthcare, and thus reduce the psychosocial impact of their disease. Benefits of support groups on quality of life and psychological outcomes in people with COPD have not yet been demonstrated, although studies of other chronically ill patient groups indicate that positive effects can be expected (Kennedy et al., 2007). One pathway to initiate attendance of support groups is through pulmonary rehabilitation programs. The likely benefits of support groups for people with COPD are summarised in **Box 7**.

### Box 8 : Patient support groups

#### Typical support group activities

- Regular meetings
- Guest speakers providing information on a range of topics
- Receiving and distributing lung health education information
- Education and information days
- Exercise programs
- Social or recreational activities
- Group newsletters
- Member to member support (through telephone calls, hospital and home visits)

#### 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

A list of Patient Support Group names and locations can be accessed via Lung Foundation Australia's website at <http://lungfoundation.com.au/patient-area/patient-support/patient-support-groups/> Contact details can be obtained from Lung Foundation Australia's Information and Support Centre (free-call 1800 654 301). In New Zealand, contact the Asthma and Respiratory Foundation of New Zealand (phone +64 4 499 4592; Internet address, <http://www.asthmanz.co.nz>).

## 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<sub>1</sub> < 25% predicted, weight loss (body mass index below 18), respiratory failure (PaCO<sub>2</sub> > 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. A study by Janssen et al (Janssen et al., 2012) in a group of 265 patients with stable severe or very severe COPD, heart failure or chronic renal failure, found that more than a third of patients changed their preferences regarding life supporting measures at least once over a period of twelve months, reinforcing the importance of regular re-evaluation of advanced care planning and advanced directives.

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](Jennings et al., 2002),(Abernethy et al., 2003)

### 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 characterised 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 (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2006)

ACUTE EXACERBATIONS of COPD which are more frequent in the winter months in temperate climates (Jenkins et al., 2012) [evidence level II] often require hospital admission for treatment of respiratory failure. A record linkage study in WA (Geelhoed et al., 2007) 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. (Connors et al., 1996) 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. (Ansari et al., 2007)

Exacerbations become more frequent as severity of COPD worsens. (Hoogendoorn et al., 2010a) In the study by the ECLIPSE investigators, exacerbation rate increased with increasing GOLD stage, such that 22% of patients with GOLD stage 2 disease had two or more exacerbations during one year of follow-up, whereas 47% of patients with GOLD stage 4 disease had frequent exacerbations over the same period. The single best predictor of exacerbations across all GOLD stages was prior exacerbations. Other predictors included a history of heartburn, poorer quality of life and elevated white cell count (Hurst et al., 2010). Studies have confirmed that although the prognosis of exacerbations is poor, it is improving. Hoogendoorn et al. (Hoogendoorn et al., 2010c) identified six cohort studies that followed the survival of COPD patients for at least 1.5 years after a severe exacerbation resulting in hospitalisation. A meta-analysis resulted in a weighted average case-fatality rate of 15.6% (95%CI 10.9-20.3). The excess risk of mortality continued after discharge from hospital. Almagro et al. (Almagro et al., 2010) prospectively examined three year mortality after a severe exacerbation resulting in hospitalisation in two well matched cohorts seven years apart (1996/97 and 2003/04). The 1996/97 three year survival rate was 53% and the 2003/4 three year survival rate was significantly improved at 61% (log rank  $p = 0.017$ ). The 2003/4 cohort had increased usage of tiotropium, long acting beta<sub>2</sub> agonists, angiotensin receptor blockers, statins and anti-platelet therapy. The authors speculated that the increased survival may be due to improved treatment options for COPD and co-morbidities including cardiac disease. [evidence level III-2]

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. (Macfarlane et al., 1993, Smith et al., 1980, Soler et al., 1998, Wilson, 1998, Stockley et al., 2000, Walsh et al., 1999, Mogulkoc et al., 1999, Murphy et al., 1999, Miravittles et al., 1999) Exacerbations can also be caused by viral infection. (Seemungal et al., 2001) Other causes include left ventricular failure and pulmonary embolus. A panel study of patients with moderate to severe COPD demonstrated that exacerbations could also be triggered by urban air pollutants such as PM<sub>10</sub>, black smoke and NO<sub>2</sub> (Peacock et al., 2011) [evidence level II]. Chest trauma and inappropriate use of sedatives can lead to sputum retention and hypoventilation. A diagnosis of pulmonary embolism should be considered in patients with an intermediate to high pretest probability of pulmonary embolism. A systematic review found one of four COPD patients who require hospitalisation for an acute exacerbation may have pulmonary embolism (Rizkallah et al., 2009) [evidence level I].

Early diagnosis and treatment may prevent admission (Wilkinson et al., 2004) [evidence level III-2]

Early diagnosis and prompt management of exacerbations of COPD may prevent progressive functional deterioration and reduce hospital admissions. (Lorig et al., 1999), (Shepperd et al., 1998) 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://lungfoundation.com.au/health-professionals/clinical-resources/copd/copd-action-plan/>). This plan might indicate which medications to take, including antibiotics and oral corticosteroids. 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(Lorig et al., 1999),(Shepperd et al., 1998),(Skwarska et al., 2000),(Kong et al., 1997) [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. Such “Hospital in the Home” schemes were studied in a systematic review by Jeppesen(Jeppesen et al., 2012) that included 8 randomised controlled trials which entered patients into a hospital in the home scheme within 72 hours of presenting to hospital. The review found that compared to standard care, participants allocated to hospital in the home were significantly less likely to be readmitted to hospital within the next 1 to 6 months (risk ratio = 0.76, 85% confidence interval 0.59 to 0.99) [evidence level I]. There was no significant difference in mortality (risk ratio = 0.65, 95% confidence interval 0.40 to 1.04), and while there was no difference in satisfaction levels for patients or carers, these comparisons were based on small numbers. Economic studies of such programs have shown mixed results.

## X2. COPD acute exacerbation management

### 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 (e.g., 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 (i.e., 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 percutaneous oxygen saturation is less than 90% in the presence of adequate peripheral perfusion or cor pulmonale. Values obtained while breathing room air are the most useful for assessing ventilation-perfusion inequality. A  $PaO_2$  less than 60 mmHg (8 kPa) indicates respiratory failure, while a  $PaCO_2$  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.

Studies have identified a simple clinical prediction score, the BAP-65, based on age, basal urea nitrogen, acute mental status change and pulse, which predict in-hospital mortality. (Tabak et al., 2009, Shorr et al., 2011) In-hospital mortality in both studies increased as patient classification escalated from 1 (no risk factors, age  $< 65$  yrs) to 5 (3 risk factors present), the highest class being associated with an in-hospital mortality between 14.1% and  $> 25\%$ .

A 2012 prospective single centre study of 920 patients admitted with an acute exacerbation of COPD found that those with CXR

confirmed pneumonia had a far higher mortality (20.1% vs 5.8%,  $p < 0.001$ ). Severity of dyspnoea in the stable state was strongly associated with both in-hospital mortality and early readmission(Steer et al., 2012) [evidence level III-2].

## 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 (e.g., salbutamol, 400–800mcg; terbutaline, 500–100mcg) and antimuscarinic agent (ipratropium, 80mcg) can be given by pressurised metered dose inhaler and spacer, or by jet nebulisation (salbutamol, 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.
- **Corticosteroids:** Oral corticosteroids 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 adverse 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% ( $\text{PaO}_2 > 50$  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 (NHLBI/WHO Workshop Report, April 2001), (Siafakas et al., 1995), (American Thoracic Society, 1995), (British Thoracic Society, 1997, Moayyedi et al., 1995, Fernandez et al., 1994) [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. (Cates et al., 2006) The applicability of this evidence to patients with COPD is unknown. There is evidence in patients with a COPD exacerbation that a dry powder inhaler delivering formoterol is as effective in improving lung function as a metered dose inhaler delivering salbutamol, with or without a spacer device (Selroos et al., 2009) [evidence level II]. 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. Limited evidence indicates dry powder inhalers are as effective as other delivery devices for the administration of short-acting bronchodilators in the setting of acute exacerbations of COPD (Selroos et al., 2009) [evidence level II]. Airflow in the nebuliser should be 6 L per minute or higher to achieve an appropriate aerosol, but using high-flow oxygen should be avoided as this may worsen carbon dioxide retention. High doses of beta-agonists may induce hypokalaemia and predispose to cardiac arrhythmias.

### X2.2.2 Systemic corticosteroids for treatment of exacerbations

Systemic corticosteroids reduce the severity of and shorten recovery from acute exacerbations (Walters et al., 2009) [evidence level I]

A meta-analysis of 11 studies found that systemic corticosteroid treatment was associated with a significantly lower 30 day treatment failure rate (NNT = 10, 95% CI 7 to 16). (Walters et al., 2009) Systemic corticosteroids significantly decreased hospital stay (mean difference = -1.22 days, 95%CI -2.26 to -0.18), improved FEV<sub>1</sub> at early and end of treatment time points, decreased breathlessness and improved arterial blood gases. There was an increased likelihood of an adverse event with systemic corticosteroids (NNH = 5, 95% CI 4 to 9), although most of these were minor in nature. Alia et al performed the first randomised controlled trial on the efficacy of corticosteroids in patients with acute exacerbations in intensive care requiring either mechanical ventilation or non-invasive ventilation (Alia et al 2011). A weaning intravenous schedule was used over a 10 day period. Although there were potential issues with blinding, the authors found a significant reduction in the median length of mechanical ventilation (3 vs. 4 days P=0.04) and a significant reduction in NIV failure (0 vs. 37% P=0.04) (Alia et al., 2011) [evidence level II].

Oral corticosteroids are recommended, for ease of administration and, as there is no evidence intravenous administration has a more rapid effect, a dose of 30-50mg of prednisolone or equivalent appears adequate. The optimal dose, route and duration of systemic corticosteroid treatment have not been established, and although a meta-analysis of seven studies including 288 participants found no significant increase in treatment failure with shorter treatment (seven days or less), there was no conclusive evidence to recommend change in clinical practice due to a wide confidence interval around the estimate of effect. (Walters et al.,

2011c) In 2013, a randomised controlled study (Leuppi et al., 2013) in over 300 Swiss patients with acute exacerbations of COPD presenting to the emergency department, found that a five day course of corticosteroids (one 40mg dose of intravenous methylprednisolone followed by four days of prednisolone 40mg) was non-inferior to treatment for 14 days (one IV dose plus 13 days of 40 mg prednisolone) with regard to subsequent exacerbation over six months of follow-up. There is no evidence that prolonging treatment beyond two weeks provides additional benefit, and tapering of treatment is not necessary for courses of systemic corticosteroids up to this duration. A pharmacoepidemiological cohort study (Lindenauer et al., 2010) [evidence level III-2] found the risk of treatment failure was significantly lower for those treated with oral compared to intravenous corticosteroids, odds ratio 0.84 (95% CI 0.75, 0.95).

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 (Isada CM and Stoller JK, 1994), (Siafakas NM and Bouros D, 1998), (Anthonisen et al., 1987, Patel et al., 2002, Seemungal et al., 2001) [evidence level II]

Bacterial infection may have either a primary or secondary role in about 50% of exacerbations of COPD. (Macfarlane et al., 1993), (Wilson, 1998), (Miravittles et al., 1999), (Patel et al., 2002) *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* are most commonly involved. (Macfarlane et al., 1993), (Soler et al., 1998), (Murphy et al., 1999) *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have also been reported. (Macfarlane et al., 1993), (Mogulkoc et al., 1999) As lung function deteriorates (FEV<sub>1</sub> < 35%), *Pseudomonas aeruginosa* and *Staphylococcus aureus* are often encountered. (Macfarlane et al., 1993), (Soler et al., 1998), (Miravittles et al., 1999) Multi drug resistant *Ps. aeruginosa* is associated with 6 fold increased risk of death (Montero et al., 2009) [evidence level III-2].

A 2012 Cochrane systematic review (Vollenweider et al., 2012) found a reduction in treatment failure in patients with severe exacerbations who were treated with antibiotics (RR 0.77; 95% CI 0.65 to 0.91; I<sup>2</sup> = 47%). Treatment failure was defined as lack of improvement in symptoms, deterioration, need for further antibiotics or death due to exacerbation. A reduction in mortality (data from one trial only) and a reduced length of stay was only seen in patients admitted to ICU. Patients treated with antibiotics experienced higher rates of diarrhoea (OR 2.62; 95% CI 1.11 to 6.17). No significant benefit for treatment failure in outpatients was found when analysis was restricted to currently available antibiotics (RR 0.80; 95% CI 0.63 to 1.01; I<sup>2</sup> = 33%).

El Moussaoui et al (El Moussaoui et al., 2008) 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]. A related systematic review (Falagas et al., 2008) found that patients receiving short courses experienced fewer adverse effects than those receiving longer courses. It would be necessary to treat 26 (95%CI 15 to 134) patients with short course antibiotics to prevent one adverse effect. However the antibiotics evaluated were late generation cephalosporins, macrolides and fluoroquinolones, which are not those recommended in Australia.

*Therapeutic guidelines: antibiotic* (Antibiotic Expert Group, 2010) recommend the use of oral agents such as doxycycline or amoxicillin (alternatively, erythromycin or roxithromycin). If patients do not respond, or if resistant organisms are suspected, amoxicillin–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. An historical population-based cohort study (Roede et al., 2008) [evidence level III-2] found that co-treatment of an acute exacerbation with oral corticosteroids and oral antibiotics significantly increased the time to subsequent exacerbations (median 312 versus 418 days, p<0.001 to next compared to oral corticosteroids alone).

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.

## X2.2.4 Combined systemic corticosteroids and antibiotics for treatment of exacerbation

A randomized placebo controlled trial (Daniels et al., 2010) has provided evidence to support the traditional practice of treating acute exacerbations with a combination of systemic corticosteroids and antibiotics. In this study, hospitalised patients were commenced on a tapering dose of prednisolone and randomised to receive doxycycline 200mg daily or placebo for 7 days. Clinical cure, defined as complete resolution of signs and symptoms, at day 10 was significantly higher in the antibiotic treated group compared to placebo (OR 1.9, 95% CI 1.2 to 3.2, NNT = 7, 95% CI 4 to 523). By day 30, the primary end point, there was no significant difference in clinical cure. Serious adverse effects occurred in 9% of the doxycycline group (7 deaths) and 5% of the placebo group (3 deaths). Medication adverse events were similar between groups, 3% in the doxycycline group and 4% in the placebo.

## 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 (e.g., ischaemic heart disease) and complications (e.g., 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 9 and 10**).

### Box 9: 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 (e.g., pneumonia) or non-pulmonary
- Altered mental status suggestive of hypercapnia
- Worsening hypoxaemia or cor pulmonale
- Newly occurring arrhythmia

### Box 10: 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 ( $\text{PaCO}_2 > 70$  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 (Young et al., 1998)

Correction of hypoxaemia to achieve a  $\text{PaO}_2$  of at least 55 mmHg (7.3 kPa) and an oxygen saturation of 88%–92% is the immediate priority. (NHLBI/WHO Workshop Report, April 2001) Where there is evidence of acute respiratory acidosis (or a rise in  $\text{PaCO}_2$ ), 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).

In the emergency setting, oxygen flow should be carefully titrated to achieve arterial oxygen saturations between 88 and 92%. Nasal cannulas, deliver a variable concentration of oxygen, but a flow of 0.5–2.0 L per minute is usually sufficient.

High flow oxygen via a Hudson mask or non-rebreather mask should be avoided, as it is rarely necessary and may lead to hypoventilation and worsening respiratory acidosis and increased mortality. A randomised study has demonstrated that in the pre-hospital emergency setting titrated oxygen via nasal cannula compared with high flow oxygen reduced mortality by 78% in COPD patients (NNH=14) (Austin et al., 2010) [evidence level II]. 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 (Ram et al., 2004) [evidence level I]

Ventilatory support with intermittent positive pressure ventilation (IPPV) should be considered in patients with rising PaCO<sub>2</sub> levels who are unable to ventilate adequately (i.e., acute or acute-on-chronic respiratory acidosis). (Meyer and Hill, 1994, Bott et al., 1993, Brochard et al., 1995, Kramer et al., 1995, Plant et al., 2000) This can be achieved non-invasively (by means of a face mask, NIPPV) or invasively through an endotracheal tube. (Rossi et al., 1985), (Esteban et al., 2000)

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 more 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. (Meyer and Hill, 1994, Bott et al., 1993, Brochard et al., 1995, Kramer et al., 1995, Plant et al., 2000) Failure to respond or further deterioration would indicate a need to consider intensive care unit admission (see Box 10 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) (Ram et al., 2004) [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. (Esteban et al., 2000) Relative contraindications (situations where NIPPV may be less effective) include life-threatening refractory hypoxaemia (PaO<sub>2</sub> < 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 39% (Wildman et al., 2009). A multi-centre Spanish study (Rivera-Fernandez et al., 2006) 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]. A multi-centre UK study (Wildman et al., 2009) that followed surviving patients up to 180 days found that 80% rated their quality of life unchanged compared to pre-admission and 96% would elect to receive the same treatment again under similar circumstances. Overall patients' functional capacity was slightly reduced at 180 days, but broadly predicted by, pre-admission function. Doctors' prediction of survivors' quality of life was pessimistic and agreed poorly with their patients rating.

Weaning from invasive ventilation can be facilitated by the use of non-invasive positive pressure ventilation. In a Cochrane meta-analysis of patients with predominantly COPD, the use of non-invasive ventilation for weaning resulted in decreased mortality (RR 0.55, 95% CI 0.38 to 0.79), reduced ventilator-assisted pneumonia (RR 0.29, 95% CI 0.19 to 0.45), reduced length of stay in ICU (WMD -6.27 days, 95% CI -8.77 to -3.78) and reduced hospital length of stay (WMD -7.19 days, 95% CI -10.8 to -3.58) (Burns et al., 2010)

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 sputum or those with tenacious sputum may benefit from airway clearance techniques (ACTs) during an exacerbation. However, the choice of ACTs during acute exacerbations requires careful consideration as these episodes result in worsening of airflow limitation and lung hyperinflation, which lead to acute increases in dyspnoea. Patients are also likely to experience significant physical fatigue during an acute exacerbation and this impacts on the choice of ACT.

A Cochrane Systematic Review of 9 trials examined the efficacy of ACTs in patients experiencing an AECOPD. (Osadnik et al., 2012) The use of ACTs was associated with a significant short-term reduction in the need for increased ventilatory assistance (odds ratio 0.21, 95% CI 0.05 to 0.85, data from 4 studies involving 171 patients) NNT 12, 95% CI 10-66 [evidence level I], the duration of ventilatory assistance (mean difference of -2.05 days, 95% CI -2.60 to -1.51 compared to control, data from 2 studies of 54 patients) [evidence level I] and hospital length of stay (mean difference -0.75 days, 95% CI -1.38 to -0.11 compared to control, data from one study of 35 patients) [evidence level II]. Airway clearance techniques that utilised positive expiratory pressure (PEP) tended to be associated with a greater reduction in the need for increased ventilatory assistance and hospital length

of stay compared to non-PEP based ACTs however the difference was not significant.

With the exception of chest wall percussion, which has been associated with a decrease in FEV<sub>1</sub> and one report of vomiting during treatment involving a head-down tilt position ACTs were not associated with serious adverse effects (Hill et al., 2010, Tang et al., 2010), (Osadnik et al., 2012) [evidence level I]. Airway clearance techniques applied during an exacerbation do not appear to improve measures of resting lung function or produce any consistent changes in gas exchange (Osadnik et al., 2012) [evidence level I]. However, the limitations of the studies included in the systematic reviews (i.e. considerable diversity in patients' characteristics and application of specific techniques, small sample sizes in some of the studies, large variety of outcome measures) limited the ability to pool data for meta-analysis. A multicentre RCT that involved 90 patients hospitalised with an AECOPD investigated whether the addition of PEP therapy to usual medical care that included a standardized physical exercise training regimen improved symptoms, QoL and incidence of future exacerbations (Osadnik et al., 2014). Individuals in this study were characterized by evidence of sputum expectoration or a history of chronic sputum production with over 50% of those recruited expectorating purulent sputum. The authors found no significant between group differences in symptoms or quality of life assessed over a 6-month period following hospital discharge. The incidence of exacerbations during the follow-up period was low and similar in both groups. The findings of this study do not support a routine role for PEP therapy even in patients with purulent sputum who are hospitalized for an AECOPD.

### 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 (SpO<sub>2</sub> 88%–92%).
- **Respiratory function testing:** FEV<sub>1</sub> 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 and has shown to be safe. (Puhan et al., 2009a) Such a program improves functional exercise capacity, health-related quality of life, and reduces unplanned hospital admissions and mortality (Puhan et al., 2009a, Puhan et al., 2011) [evidence level I].

A list of pulmonary rehabilitation programs known to Lung Foundation Australia can be accessed at <http://lungfoundation.com.au/patient-area/resources/pulmonary-rehabilitation/pulmonary-rehabilitation-programs-2/>. The individual contact details can be obtained by calling the Lung Foundation's Information and Support Centre (free-call 1800 654 301).

### 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 10**). 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. See <http://www.health.gov.au/internet/main/publishing.nsf/Content/mbsprimarycare-chronicdiseasemanagement-qanda>

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 8: 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 (e.g., 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 and supported discharge programs are now well established. Such programs are generally short term in nature and have clear criteria for which patients are suitable. Compared to more traditional in-patient management, supported discharge programs are associated with shorter length of stay and lower 90-day mortality, with little difference in readmission rate (Kastelik et al., 2012), confirming the safety of such an approach. Over the longer term, 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 (Casas et al., 2006) (evidence level II). However, a study of supported self-management following discharge, which combined home visits to empower participants to manage their COPD independently and case management to facilitate prompt and appropriate access to care, did not find any significant benefit on COPD admissions or death when compared to usual care (hazard ratio = 1.05, 95% confidence interval 0.08 to 1.38). (Bucknall et al., 2012) Not only do these studies have different outcomes, they were conducted in Europe and their applicability to the Australasian setting is not known. 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.

### X3.9 Clinical review and follow-up

There are no randomised clinical trials that have addressed the best method for follow-up. (Sin et al., 2002) It is recommended that the first review after a hospital admission should be by the GP and within seven days of discharge (Box 11). Chronic cough and sputum production is associated with an increased risk of further exacerbation (Burgel et al., 2009) [evidence level III-2] and these patients may warrant closer monitoring. 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. (Sin et al., 2002)

### Box 9: Follow-up – initial and subsequent

- Assessment of the patient's coping ability and strategies
- Measurement of FEV<sub>1</sub> and performance status
- Reassessment of medication adherence and techniques with inhalation devices
- Review of immunisation 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 corticosteroids determined in response trials

Response	Drug	Dose (mcg)	Frequency	Delivery
Improved airway function Improved exercise capacity Reduced breathlessness Improved quality of life	<b>beta-Agonist</b>			
	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
	<b>Anticholinergic (Antimuscarinic)</b>			
	Ipratropium	40-80mcg	6-8-hourly	MDI/spacer
	Tiotropium	18mcg	24-hourly	DPI
	<b>Corticosteroid</b>			
	Beclomethasone (small particle)	400-800mcg/day		Inhaled MDI/spacer
	Budesonide	800-1600mcg/day		DPI
	Fluticasone	500-1000mcg/day		MDI/DPI
	Ciclesonide	80-320mcg/day		MDI – spacer not recommended

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

## Appendix 2. Explanation of inhaler devices

Delivery system	Available products	Considerations
<b>Metered dose inhaler (MDI)</b>	Ventolin, Asmol, Airomir, Epaq (salbutamol 100mcg); Atrovent (ipratropium bromide 21mcg); Qvar (beclomethasone 50mcg, 100mcg); Alvesco (ciclesonide 80mcg, 160mcg); Flixotide (fluticasone 50mcg, 125mcg, 250mcg); Serevent (salmeterol 25mcg); Seretide (salmeterol 25mcg and fluticasone 50mcg, salmeterol 25mcg and fluticasone 125mcg, salmeterol 25mcg and fluticasone 250mcg); Symbicort Rapihaler (budesonide 200 mcg and eformoterol 6 mcg)	<ul style="list-style-type: none"> <li>MDIs should be used with a spacer device, as some people have difficulty coordinating the release of medication with inhalation.</li> </ul>
<b>Spacers</b>	Aerochamber Breath-A-Tech Fisonair Nebuhaler Volumatic	<ul style="list-style-type: none"> <li>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.</li> <li>Use of spacers with inhaled corticosteroids reduces adverse effects of oral candidiasis and hoarseness, as well as optimising medication delivery.</li> <li>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.</li> <li>Spacers are cheap, portable, easily cleaned and maintained, do not require electricity and are simple and quick to use.</li> <li>A small volume spacer is preferable when the vital capacity is less than 1.5L.</li> </ul>
<b>Autohaler</b>	Airomir (salbutamol 100mcg); Qvar (beclomethasone 50mcg, 100mcg)	<ul style="list-style-type: none"> <li>Breath-activated MDI containing 200 doses of medication.</li> <li>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.</li> </ul>
<b>Dry powder inhalers (DPI)</b>		
Accuhaler	Serevent (salmeterol 50mcg); Flixotide (fluticasone 100mcg, 250mcg, 500mcg); Seretide (salmeterol 50mcg and fluticasone 100mcg, salmeterol 50mcg and fluticasone 250mcg, salmeterol 50mcg and fluticasone 500mcg)	<ul style="list-style-type: none"> <li>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).</li> <li>Lactose powder is combined with the active medication for patients to taste and reassure them that they have inhaled a dose.</li> </ul>
Aerolizer	Foradile (formoterol 12mcg)	<ul style="list-style-type: none"> <li>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.</li> <li>Gives consistent drug delivery over a range of inspiratory flow rates.</li> </ul>
Turbuhaler	Bricanyl (terbutaline 500mcg); Pulmicort (budesonide 100mcg, 200mcg, 400mcg); Oxis (formoterol 6mcg, 12mcg); Symbicort (formoterol 6mcg and budesonide 100mcg, formoterol 6mcg and budesonide 200mcg, formoterol 12mcg and budesonide 400mcg)	<ul style="list-style-type: none"> <li>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.</li> <li>Dose delivery is halved if the patient cannot produce inspiratory flow above 30L/min. Very few patients with COPD cannot produce a rate of &gt;60L/min.</li> <li>Produces very fine powder, so patients often don't taste anything.</li> <li>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</li> </ul>

HandiHaler	Spiriva (tiotropium 18mcg)	<p>medication).</p> <ul style="list-style-type: none"> <li>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.</li> </ul>
Breezhaler	Onbrez (indacaterol 150mcg, 300 mcg)	<ul style="list-style-type: none"> <li>Breath-activated single-dose powder inhaler</li> <li>Capsules come in foil packs containing 30 capsules in a cardboard carton</li> <li>Breezhaler inhalation device allows oral inhalation of the content of the capsule shell. One capsule is loaded into the inhaler and pierced before inhaling.</li> <li>Gives consistent drug delivery over a range of inspiratory flow rates.</li> </ul>
Genuair	Bretaris (aclidinium 322 microgram/ dose)	<ul style="list-style-type: none"> <li>Breath activated multi-dose DPI (containing 30 or 60 doses) with an integral dose indicator, a green dosage button and a coloured control window. Before inhaling the dose the green button should be pressed all the way down and then released. The coloured control window changes to green suggesting the dose is ready for inhalation. If the full dose is inhaled correctly, the control window turns red. Genuair is equipped with a dose indicator, displaying intervals of 10 (60, 50, 40, 30, 20, 10, 0). When a red striped band appears in the dose indicator, only a few doses are left in the device. Bretaris Genuair also contains lactose.</li> </ul>
Ellipta	Breo (Fluticasone furoate 100 or 200 micrograms and vilanterol trifenate 25 micrograms/dose)	<ul style="list-style-type: none"> <li>Breath activated multi-dose DPI containing 14 or 30 doses. The active substances are in separate blisters in powder form inside the device. It has a dose counter; when fewer than 10 doses are left, half of the dose counter shows red.</li> </ul>
<b>Nebulisers</b>	<p>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 corticosteroids requires a high-flow, heavy-duty pump.</p>	<ul style="list-style-type: none"> <li>Corticosteroid or ipratropium bromide aerosol should not be allowed to enter the eyes to avoid the risk of adverse 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.</li> <li>Ipratropium can be combined with beta-agonist, but not with corticosteroid.</li> </ul>

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The products listed are not all subsidised under the Pharmaceutical Benefits Scheme for use in COPD.

## Appendix 3. Long term oxygen therapy (McDonald et al., 2005)

### Initiating oxygen therapy

- Before introducing oxygen therapy, ensure optimal treatment of the pulmonary disorder while monitoring improvement with objective tests such as FEV<sub>1</sub> 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<sub>2</sub> > 60 mmHg, or 8 kPa; SpO<sub>2</sub> > 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<sub>2</sub> of 60 mmHg (8kPa) or SpO<sub>2</sub> > 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<sub>2</sub> 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<sub>2</sub> and PaCO<sub>2</sub>, 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<sub>2</sub> < 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 PaCO<sub>2</sub> may depress ventilation, increase physiological dead space, and further increase arterial PaCO<sub>2</sub>. This is suggested by the development of somnolence, headache and disorientation.
- In long-term oxygen therapy, the increase in arterial PaCO<sub>2</sub> 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 (e.g., 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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