

The COPDX Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2015

Current COPD-X Guidelines Committee

Professor Ian Yang, MBBS(Hons), PhD, FRACP, Grad Dip Clin Epid, Thoracic Physician, The Prince Charles Hospital; School of Medicine, The University of Queensland, Brisbane (Chair)

Dr Eli Dabscheck, MBBS, M Clin Epi, FRACP, Staff Specialist, Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, Melbourne, VIC (Deputy Chair)

Dr Johnson George, BPharm, MPharm, PhD, Grad Cert Higher Education, Senior Lecturer, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, VIC

Associate Professor Sue Jenkins, GradDipPhys, PhD, School of Physiotherapy, Curtin University; Physiotherapy Department, Sir Charles Gairdner Hospital, Perth, WA

Professor Christine F McDonald, MBBBS(Hons), PhD, FRACP, Director, Department of Respiratory and Sleep Medicine, Austin Hospital, Melbourne, VIC

Associate Professor Vanessa McDonald (DipHlthScien (Nurs), BNurs, PhD, Centre for Asthma and Respiratory Disease, School of Nursing and Midwifery, The University of Newcastle; Academic Clinician, Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, NSW

Professor Brian Smith, MBBS, Dip Clin Ep & Biostats, PhD, FRACP, Thoracic Physician, The Queen Elizabeth Hospital, Adelaide, SA

Professor Nick Zwar, MBBS, MPH, PhD, FRACGP, Professor of General Practice, School Public Health & Community Medicine, Faculty of Medicine, University of New South Wales, Sydney

Lung Foundation Australia administrative support

Ms Juliet L Brown, BA(Hons), MLib, Executive Officer, COPD-X Guidelines Committee, Lung Foundation Australia, Brisbane

Ms Elizabeth A Harper, BAppSce(AppChem), Director COPD National Program, Lung Foundation Australia, Brisbane

Website Support

Ms Karen Lather, Project Manager, Lung Foundation Australia, Brisbane

Literature Searches

Ms Megan Neumann, Librarian, The Prince Charles Hospital, Brisbane

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.

Correspondence: Lung Foundation Australia, PO Box 1949, Milton QLD 4064. enquiries@lungfoundation.com.au

Past Committee Members

Past Chairpersons

Professor Michael Abramson, MBBS, BMedSc(Hons), PhD, FRACP, FAFPHM, Deputy Head, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC (Principal Author) (Chair: 2004-2014)

Professor Alan J Crockett, PSM, MPH, PhD, FANZSRS Professor of Clinical Respiratory Physiology, Division of Health Sciences, University of South Australia; Emeritus Fellow, Discipline of General Practice, School of Population Health, University of Adelaide, Adelaide, SA (Chair: 2003-2004)

Past Committee Members

Associate Professor David K McKenzie, PhD, FRACP, Director of Cardiac and Respiratory Services, South East Sydney Local Health District and Head of Department, Respiratory and Sleep Medicine, Prince of Wales Hospital, Randwick, NSW (Principal author)

Professor Peter A Frith, MBBS, FRACP, Professor in Respiratory Medicine, Flinders University and Repatriation General Hospital, Daw Park, SA

Professor Norbert Berend, MD, FRACP, Director, Woolcock Institute of Medical Research, Royal Prince Alfred Hospital, Sydney, NSW

Ms Jenny Bergin, BPharm, MPS, Pharmacist Consultant, Pharmacy Guild of Australia

Dr Jonathan G W Burdon, MD, FRACP, Respiratory Physician, Department of Respiratory Medicine, St Vincent's Hospital, Melbourne, VIC

Associate Professor Stephen Cala, PhD, FRACP, Respiratory Physician, and Head, Respiratory Investigation Unit, Gosford Hospital and University of Newcastle, NSW

Associate Professor Peter Gibson, MBBS, FRACP, Respiratory Specialist, John Hunter Hospital, Newcastle, NSW

Professor Nicholas Glasgow, MBChB, MD, FRNZGP, FRACGP, FACHPM, Dean, Medicine and Health Sciences, College of Medicine, Biology and Environment, the Australian National University, Canberra, ACT

Dr Christine Jenkins, AM, MD, FRACP, Thoracic Physician, Concord Hospital, Sydney, NSW

Mr Ross Lisle, Consumer Representative, Toowoomba, QLD

Professor Guy Marks, Australian Centre for Asthma Management, Sydney, NSW

Dr Jitendra Parikh, MD, MPM, Royal Australian College of General Practitioners

Professor Harold H Rea, MD, FRACP, Academic Head of Medicine, South Auckland Clinical School, University of Auckland, New Zealand

Mrs Marilyn Robinson, RN, Respiratory/Asthma Educator, Townsville Community Health Service, Townsville Health Services District, QLD

Professor Julian A Smith, MS, FRACS, Professor, and Head, Department of Surgery, Monash University, and Head, Cardiothoracic Surgery Unit, Monash Medical Centre, Clayton, VIC

Associate Professor Greg. Snell, MBBS, FRACP, Respiratory and Lung Transplant Physician, Department of Respiratory Medicine, Alfred Hospital, Melbourne, VIC

Associate Professor Robin D Taylor, MD, FRCPC, Department of Respiratory Medicine, Dunedin School of Medicine, University of Otago, Dunedin, NZ

Professor G Ian Town, DM, FRACP, Dean, Christchurch School of Medicine and Health Sciences, New Zealand

Mr Marcus Weidinger, Pharmaceutical Society of Australia

Dr Richard Wood-Baker, MBBS, DM, FRACGP, FRCP, MRCP[1], MEd, Director of Cardiorespiratory Medicine, Royal Hobart Hospital; Honorary Fellow, Menzies Research Institute, Hobart, TAS

Other contributors – Past and Present

Associate Professor Jenny Alison, Physiotherapist, Sydney, NSW

Dr Guy Bannink, Staff Specialist Palliative Medicine, Dept Health and Human Services, Hobart, TAS

Mr Paul Cafarella, Psychologist, Adelaide, SA

Associate Professor Donald Campbell, Respiratory Physician, Melbourne, VIC

Dr Belinda Cochrane, Staff Specialist Respiratory and Sleep Physician, Sydney, NSW

Dr Karen Detering, Respiratory Physician, Melbourne, VIC

Dr Tanja Effing, Respiratory Scientist/ Epidemiologist, Adelaide, SA

Dr Michael Epton, Respiratory Physician, Christchurch, New Zealand

Dr David Hart, Respiratory Physician, Melbourne, VIC

Associate Professor Peter Holmes, Respiratory Physician, Melbourne, VIC

Dr Alice YM Jones, Honorary Professor, Faculty of Health Sciences, University of Sydney, NSW; Adjunct Professor, School of Allied Health, Griffith University, QLD; Honorary Professor, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong

Dr Kirk Kee, Respiratory Physician, Melbourne, VIC

Ms Leona Knapman, Exercise Physiologist, Melbourne, VIC

Associate Professor John Kolbe, Respiratory Physician, Auckland, New Zealand

Dr Tom Kotsimbos, Respiratory Physician, Melbourne, VIC

Dr Nicole Livermore, Senior Clinical Psychologist, Sydney, NSW

Ms Maria Loder, Respiratory Nurse, Melbourne, VIC

Dr James Markos, Respiratory Physician, Hobart, TAS

Dr R Doug McEvoy, Director, Adelaide Institute for Sleep Health, Adelaide, SA

Dr Ruth McKenzie, General Practitioner, Sydney, NSW

Dr Lucy Morgan, Respiratory Physician, Sydney, NSW

Dr Shirley PC Ngai, Assistant Professor, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong

Dr Matthew Peters, Respiratory Physician, Sydney, NSW

Associate Professor Phillippa Poole, Senior Lecturer, Auckland, New Zealand

Professor Robert Pierce, Respiratory Physician, Melbourne, VIC

Associate Professor Robyn Richmond, School of Community Medicine, University of New South Wales, Sydney, NSW

Dr Jonathan Rutland, Respiratory Physician, Sydney, NSW

Professor Paul Seale, Respiratory Physician, Sydney, NSW

Ms Laura Smith, PhD Student, Adelaide, SA

Ms Sheree Smith, Respiratory Nurse, Brisbane, QLD

Ms Gillian Syres, Research Fellow, Melbourne, VIC

Mr Pieter Walker, Psychologist, Melbourne, VIC

Professor Trevor Williams, Clinical Director, Melbourne, VIC

A/Prof Lisa Wood, School of Biomedical Science and Pharmacy, Faculty of Health and Medicine, University of Newcastle, NSW

Associate Professor Iven Young, Respiratory Physician, Sydney, NSW

Table of Contents

Current COPD-X Guidelines Committee	1
Lung Foundation Australia administrative support.....	1
Website Support	1
Past Committee Members	2
Past Chairpersons	2
Past Committee Members	2
Other contributors – Past and Present	3
Foreword	9
The origins of the COPD-X guidelines.....	10
Levels of evidence	11
Executive Summary of the COPDX guidelines	12
<i>C: Case finding and confirm diagnosis</i>	14
C1. Aetiology and natural history.....	15
C1.1 Natural history	18
C2. Diagnosis	19
C2.1 History	19
C2.2 Physical examination.....	20
C2.3 Spirometry	21
C2.4 Flow volume tests	23
C2.5 COPD screening devices for targeted case finding	23
C3. Assessing the severity of COPD	23
C4. Assessing acute response to bronchodilators.....	24
C4.1 Confirm or exclude asthma.....	25
C5. Specialist referral	25
C5.1 Complex lung function tests	26
C5.2 Exercise testing	26
C5.3 Sleep studies	26
C5.4 Chest x-rays	26
C5.5 High resolution computed tomography.....	27
C5.6 Ventilation and perfusion scans	27
C5.7 Transcutaneous oxygen saturation	27
C5.8 Arterial blood gas measurement.....	27
C5.9 Sputum examination.....	27
C5.10 Haematology and biochemistry.....	27

C5.11 Electrocardiography and echocardiography	28
C5.12 Trials of Therapy	28
<i>O: Optimise function</i>	30
O1. Inhaled bronchodilators	31
O1.1 Short-acting bronchodilators	31
O1.1.1 Short-acting beta₂-agonists (SABA)	31
O1.1.2 Short-acting muscarinic antagonist (SAMA)	31
O1.1.3 Short-acting bronchodilator combinations	32
O1.2 Long-acting bronchodilators	32
O1.2.1 Long-acting muscarinic antagonists (LAMA)	32
O1.2.2 Long-acting beta₂-agonists (LABA)	34
O1.2.3 Long-acting bronchodilator combinations (LAMA/LABA)	35
O1.3 Assessment of response and continuation of bronchodilator therapy	36
O2. Oral bronchodilators	36
O2.1 Methylxanthines	36
O2.2 Phosphodiesterase type-4 inhibitors	36
O3. Corticosteroids	37
O3.1 Oral corticosteroids	37
O3.2 Inhaled corticosteroids (ICS)	37
O3.3 Inhaled corticosteroids versus long-acting beta₂-agonists	39
O4. Inhaled combination therapy	39
O4.1 Inhaled corticosteroids and long-acting beta₂-agonists in combination (ICS/LABA)	39
O4.2 Inhaled corticosteroids and long-acting beta-agonists and long-acting anticholinergics (antimuscarinics) in combination	41
O5. Inhaler technique and adherence	41
O6. Non-pharmacological interventions	42
O6.1 Physical activity	42
O6.2 Exercise training	42
O6.3 Education and self-management	43
O6.3.1 Psychosocial support	44
O6.4 Pulmonary rehabilitation	44
O6.5 Breathing exercises	45
O6.6 Chest physiotherapy (Airway clearance techniques)	46
O6.7 Smoking cessation	46

O6.8 Nutrition	47
O6.9 Complementary and alternative therapies	50
O7. Comorbidities	50
O7.1 Increased risks from comorbidities in the presence of COPD	50
O7.2 Cardiac disease	51
O7.2.1 Heart failure	53
O7.2.2 Safety of beta-blockers	54
O7.2.3 Statins	55
O7.2.4 Coronary revascularisation procedures	55
O7.3 Osteoporosis	56
O7.4 Sleep related breathing disorders	57
O7.5 Aspiration	57
O7.6 Gastro-oesophageal reflux disease (GORD)	58
O7.7 Lung cancer	58
O7.8 Alcohol and sedatives	59
O7.9 Testosterone deficiencies and supplementation	59
O7.10 Cognitive impairment	59
O7.11 Anaemia	60
O8. Hypoxaemia and pulmonary hypertension	60
O8.1 Treatment	62
O9. Surgery	63
O9.1 Bullectomy	63
O9.2 Lung volume reduction surgery and other techniques	63
O9.3 Lung Transplantation	64
O10. Palliation and end of life issues	65
O10.1 Opioids	65
O10.2 Advanced Care Plans	66
O10.3 Palliative oxygen therapy for dyspnoea	66
<i>P: Prevent deterioration</i>	67
P1. Risk factor reduction	67
P1.1 Smoking cessation	67
P1.2 Treatment of nicotine dependence	68
P1.2.1 Nicotine replacement therapy	69
P1.2.2 Antidepressants	69
P1.2.3 Nicotine receptor partial agonists	70

P1.2.4 Other agents	71
P1.2.5 Electronic cigarettes (e-cigarettes)	71
P1.3 Prevent smoking relapse	72
P2. Immunisations	72
P2.1 Influenza immunisation	72
P2.2 Pneumococcal immunisation	72
P2.3 Haemophilus influenzae immunisation	73
P3. Immuno-modulatory agents	73
P4. Antibiotics	73
P5. Long-acting bronchodilators	74
P5.1 Anticholinergics (Antimuscarinics)	74
P5.2 Comparison of Inhaled Medications	74
P6. Corticosteroids	75
P7. Mucolytic agents	75
P8. Humidification therapy	75
P9. Regular review	76
P10. Oxygen therapy	76
P10.1 Fitness to fly	78
P11 Alpha1-antitrypsin deficiency	78
<i>D: Develop a plan of care</i>	79
D1. Support team	80
D1.1 General Practitioner	80
D1.2 Other specialist physicians	81
D1.3 GP practice nurse / nurse practitioner / respiratory educator / respiratory nurse	81
D1.4 Physiotherapist	81
D1.5 Occupational therapist	81
D1.6 Social worker	81
D1.7 Clinical psychologist / psychiatrist	81
D1.8 Speech pathologist / therapist	82
D1.9 Pharmacist	82
D1.10 Dietitian / Nutritionist	82
D1.11 Exercise physiologist	82
D1.12 Non-medical care agencies	82
D2. Multidisciplinary care plans	83
D3. Self-management	83

D3.1 Maintenance therapy	84
D3.2 Exacerbations and crises	84
D4. Telehealth	84
D5. Treat anxiety and depression	85
D6. Referral to a support group	86
D7. End-of-life issues	87
D7.1 Palliative care services	87
X: Manage eXacerbations	88
X1. Home management	89
X2. COPD acute exacerbation management	89
X2.1 Confirm exacerbation and categorise severity	89
X2.2 Optimise treatment	90
X2.2.1 Inhaled bronchodilators for treatment of exacerbations	91
X2.2.2 Systemic corticosteroids for treatment of exacerbations	91
X2.2.3 Antibiotics for treatment of exacerbations	92
X2.2.4 Combined systemic corticosteroids and antibiotics for treatment of exacerbation	93
X3. Refer appropriately to prevent further deterioration ('P')	93
X3.1 Controlled oxygen delivery	94
X3.2 Non-invasive positive pressure ventilation	94
X3.3 Invasive ventilation (intubation)	95
X3.4 Clearance of secretions	95
X3.5 Develop post-discharge plan and follow-up	96
X3.6 Pulmonary rehabilitation	96
X3.7 Discharge planning	96
X3.8 Support after discharge	97
X3.9 Clinical review and follow-up	98
Appendix 1. Use and doses of long-term inhaled bronchodilator and corticosteroids determined in response trials	99
Appendix 2. Explanation of inhaler devices	100
Appendix 3. Long term oxygen therapy (McDonald et al., 2005)	102
List of Figures	104
List of Boxes	104
References	105

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":

- Case finding and confirm diagnosis,
- Optimise function,
- Prevent deterioration,
- Develop a plan of care
- Manage eXacerbations.

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

The origins of the COPD-X 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) and access to them was advertised in a national newspaper. The draft guidelines were circulated to all members of the TSANZ and Australian Divisions of General Practice. All comments received were reviewed by the Steering Committee. The Guidelines were then published as a supplement to The Medical Journal of Australia in March 2003.

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

Associate Professor David K McKenzie and Professor Peter Frith.
Principal authors and members of the COPD Implementation Committee.
July 2005

Logistical and financial support for the development of these guidelines was provided by Lung Foundation Australia as part of its COPD program. This program is funded by non-tied program support grants from Boehringer Ingelheim Pty Ltd (North Ryde, NSW), GlaxoSmithKline Australia Pty Ltd (Boronia, VIC), Pfizer Australia (West Ryde, NSW) and Air Liquide Healthcare Pty Ltd (Alexandria, NSW).

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: Case finding and confirm diagnosis	Evidence level
- Smoking is the most important risk factor in the development of COPD - Consider COPD in all smokers and ex-smokers over the age of 35 years - The diagnosis of COPD rests on the demonstration of airflow limitation which is not fully reversible - It is important in general practice settings to obtain accurate spirometric assessment - If airflow limitation is fully or substantially reversible (FEV₁ response to bronchodilator >400ml), the patient should be treated as for asthma - Consider COPD in patients with other smoking-related diseases	I II II III-3 I
O: Optimise function	
- Inhaled bronchodilators provide symptom relief and may increase exercise capacity - Long term use of systemic corticosteroids is not recommended - Inhaled corticosteroids should be considered in patients with moderate to severe COPD and frequent exacerbations - 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 - Pulmonary rehabilitation reduces hospitalisation and has been shown to be cost-effective - Prevent or treat osteoporosis - Identify and treat hypoxaemia and pulmonary hypertension - In selected patients, a surgical approach may be considered for symptom relief	I I I I II I III-2
P: Prevent deterioration	
- Smoking cessation reduces the rate of decline of lung function - Treatment of nicotine dependence is effective and should be offered to smokers in addition to counselling - Influenza immunisation reduces the risk of exacerbations, hospitalisation and death - Mucolytics may reduce the frequency and duration of exacerbations - Long-term oxygen therapy (>15h/day) prolongs life in hypoxaemic patients (PaO₂<55mmHg, or 7.3kPa)	I I I II I
D: Develop a plan of care	
- COPD imposes handicaps which affect both patients and carers - Enhancing quality of life and reducing handicap requires a support team - Patients and their family/friends should be actively involved in a therapeutic partnership with a range of health professionals - Multidisciplinary care plans and individual self-management plans may help to prevent or manage crises - Patients who take appropriate responsibility for their own management may have improved outcomes - Anxious and depressive symptoms and disorders are common comorbidities in people with COPD	II II III-2 III-1 I
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 - Early diagnosis and treatment may prevent admission - Multidisciplinary care may assist home management - Inhaled bronchodilators are effective treatments for acute exacerbations - Systemic corticosteroids reduce the severity of and shorten recovery from acute exacerbations	III-2 II I I

- | | |
|---|----|
| <ul style="list-style-type: none"> • Exacerbations with clinical signs of infection (increased volume and change in colour of sputum and/or fever, leukocytosis) benefit from antibiotic therapy | II |
| <ul style="list-style-type: none"> • Controlled oxygen delivery (28%, or 0.5-2.0L/min) is indicated for hypoxaemia | |
| <ul style="list-style-type: none"> • Non-invasive positive pressure ventilation is effective for acute hypercapnic ventilatory failure | I |
| <ul style="list-style-type: none"> • Involving the patient's general practitioner in a case conference and developing a care plan may facilitate early discharge | |

C: Case finding and confirm diagnosis

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

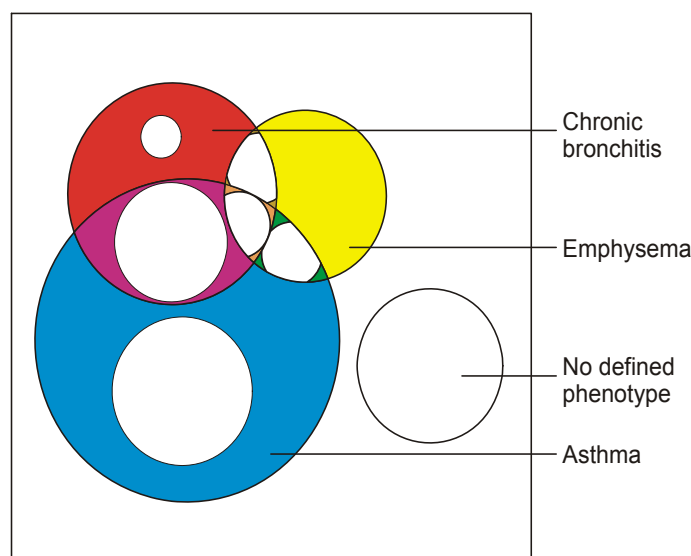
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation which is not fully reversible. The airflow limitation 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

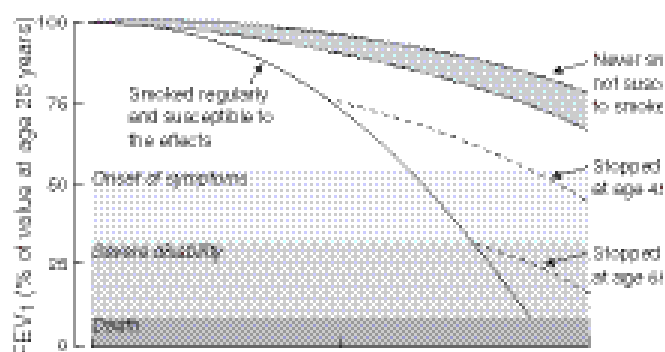
Cigarette smoking is the most important cause of COPD.(Fletcher and Peto, 1977),(Burrows et al., 1977) There is a close relationship between the amount of tobacco smoked and the rate of decline in forced expiratory flow in one second (FEV_1), although individuals vary greatly in susceptibility.(Fletcher 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_1 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**.

The annual decline in FEV_1 has been measured in 5041 patients with moderate to very severe COPD followed for 4 years (Tashkin et al., 2013). The decline in post-bronchodilator measurements was greater than pre-bronchodilator, which might represent progression of disease or tachyphylaxis [evidence level III-2].

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

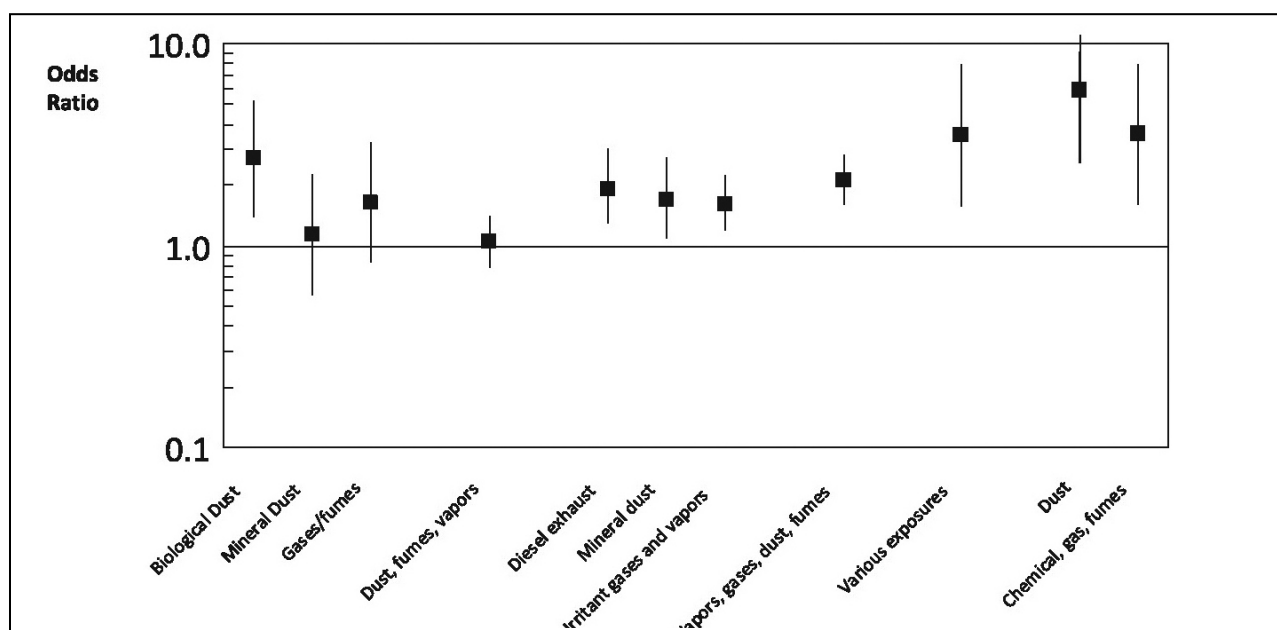


The figure (adapted from Fletcher C and Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;1:1645-1648 and reproduced with permission from the BMJ Publishing Group) shows the rate of loss of forced expiratory flow in one second (FEV₁) for a hypothetical, susceptible smoker, and the 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 FEV₁ 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, Omland et al., 2014) (see **Box 2** below adapted from GOLD 2006). COPD almost always arises from a gene environment interaction. The best characterised genetic predisposition is alpha₁ 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 phlegm and increased rate of decline in FEV₁ 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 meta-analysis of 6 cross-sectional studies found that occupational exposure to respirable quartz dust was associated with a pooled reduction in FEV₁ of -4.62 (95% CI -7.18, -2.06) %predicted (Bruske et al., 2014). 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]. Evidence of emphysema and gas trapping on CT scans was associated with self-reported occupational exposures to dust and fumes in both men and women who were former

or current smokers (Marchetti et al., 2014) 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_{2.5} and NO₂ (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. There is some evidence that women might be more susceptible to the effects of tobacco smoke. ((Aryal et al., 2014)[evidence level III-2]. Beyond the age of 45-50 years, female smokers appear to experience an accelerated decline in FEV₁ 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 FEV₁ 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 VO₂ 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 FEV₁ 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 FEV₁, 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., 2009c) [evidence level III-2]. Further studies are awaited including validation in an Australian cohort of COPD patients. Nonetheless, FEV₁ 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 FEV₁ <20% predicted, 30% for those with FEV₁ of 20%–29% predicted and about 50% for those with an FEV₁ of 30%–39% predicted.(Connors et al., 1996) Patients with an FEV₁ <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 FEV₁: $r = -0.24$, $p < 0.0001$ and there was no difference in this relationship between men and women. However, a significantly faster deterioration in the SGRQ score relative to FEV₁ % 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 (Pco₂) >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. A systematic review ([Gupta et al., 2014](#)) that included 36 studies carried out in 32 countries reported the CAT to be reliable, valid and responsive as a HRQoL instrument. However, the minimum clinically important difference in the total CAT score is unclear. 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

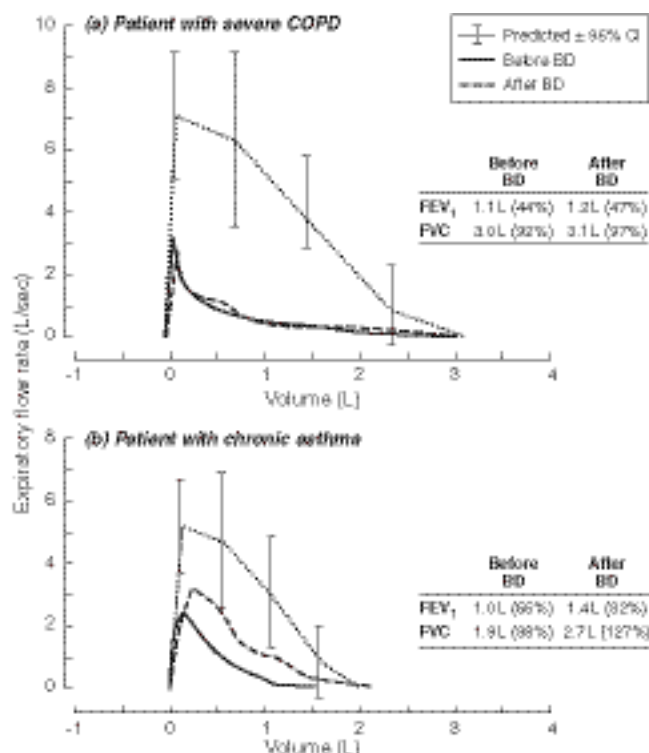
The diagnosis of COPD rests on the demonstration of airflow limitation which is not fully reversible (NHLBI/WHO Workshop Report, April 2001) [evidence level II]

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_1/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_1 to forced vital capacity (FVC) is $< 70\%$ and the FEV_1 is $< 80\%$ of the predicted value. The ratio of FEV_1 to vital capacity (VC) is a sensitive indicator for mild COPD. FEV_1/FEV_6 has a high level of agreement with FEV_1/FVC on both the fixed ratio and Lower Limit of Normal (LLN) criteria for the diagnosis of COPD. (Bhatt et al., 2014a). There is controversy regarding the optimal cut-off to define airflow limitation (FEV_1/FVC less than 0.7 vs lower limit of normal). There is conflicting data comparing the two cut-offs regarding mortality and healthcare utilisation, however a study (Bhatt et al., 2014b) shows that the fixed cut-off of 0.7 identified more people with CT diagnosed emphysema.

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 (FEV₁) was within the normal range (82% predicted). Absolute and per cent predicted values for FEV₁ 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 FEV₁ 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 (FEV₁, FEV₆) and calculate FEV₁/FEV₆, 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 FEV₁/FEV₆ cut-off < 0.75. Symptomatic or at-risk individuals with an FEV₁/FEV₆ ratio < 0.75 should undergo formal diagnostic spirometry. Symptomatic or at-risk individuals with an FEV₁/FEV₆ 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.[†]

C3. Assessing the severity of COPD

Spirometry is the most reproducible, standardised and objective way of measuring airflow limitation, and FEV₁ is the variable most closely associated with prognosis.(Peto et al., 1983) The grades of severity according to FEV₁ and the likely symptoms and complications are shown in **Box 4**. However, it should be noted that some patients with an FEV₁ >80% predicted, although within the normal range, may have airflow limitation (FEV₁/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).

[†] Level of evidence could not be assigned due to heterogeneity

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

	MILD	MODERATE	SEVERE
Typical Symptoms	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	
Lung Function	FEV ₁ ≈ 60-80% predicted	FEV ₁ ≈ 40-59% predicted	FEV ₁ < 40% predicted

FEV₁=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 FEV₁ 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 FEV₁ 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 FEV₁ 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_1 <80% predicted and FEV_1/FVC ratio <0.70 shows airflow limitation.
- Give the bronchodilator by metered dose inhaler (MDI) through a spacer device or by nebuliser.
- Give short-acting beta-agonist, at a dose selected to be high on the dose-response curve (e.g., 200–400mcg salbutamol from MDI and spacer).

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

FEV_1 =forced expiratory flow in one second.

FVC=forced vital capacity.

C4.1 Confirm or exclude asthma

If airflow limitation is fully or substantially reversible, (FEV_1 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 ₁	Optimise management
Moderate or severe COPD	Optimise management
Onset of cor pulmonale	Confirm diagnosis and optimise treatment
Assessment of home oxygen therapy: ambulatory or long-term oxygen therapy	Optimise management, measure blood gases and prescribe oxygen therapy
Assessing the need for pulmonary Rehabilitation	Optimise treatment and refer to specialist or community-based rehabilitation service
Bullous lung disease	Confirm diagnosis and refer to medical or surgical units for bullectomy
COPD <40 years of age	Establish diagnosis and exclude alpha1-antitrypsin deficiency
Assessment for lung transplantation or lung volume reduction surgery	Identify criteria for referral to transplant Centres
Frequent chest infections	Rule out co-existing bronchiectasis
Dysfunctional breathing	Establish diagnosis and refer for pharmacological and non-pharmacological management

FEV₁, 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 FEV₁ is <40% predicted or <1L, whose oxygen saturation as measured by pulse oximetry [SpO₂] is <92%), those with pulmonary hypertension, and those with breathlessness out of proportion to their clinical status). Respiratory failure is defined as a PaO₂<60mmHg (8kPa) or PaCO₂ >50mmHg (6.7kPa). The latter is termed 'ventilatory failure' and is accompanied by either compensated (chronic) or uncompensated (acute) acidosis. Acute respiratory acidosis indicates a need for assisted ventilation.

C5.9 Sputum examination

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

C5.10 Haematology and biochemistry

Polycythaemia should be confirmed as being secondary to COPD by blood gas measurement that demonstrates hypoxaemia. The possibility of sleep apnoea or hypoventilation should be considered if polycythaemia is present but oxygen desaturation or hypoxaemia on arterial blood gas tests are absent when the patient is awake.

Hyperthyroidism and acidosis are associated with breathlessness. Hyperventilation states are associated with respiratory alkalosis. Hypothyroidism aggravates obstructive sleep apnoea. Harrison

et al 2014 performed a multicentre prospective study of acute exacerbations of COPD requiring hospital admission in 1343 patients with spirometry confirmed COPD. The authors reported the novel finding of an association between thrombocytosis ($>400/\text{mm}^3$ on admission) and mortality. Thrombocytosis (after controlling for confounders) was associated with an increased 1 year all-cause mortality and an increased in hospital mortality (OR 1.53 (95% CI 1.03 to 2.29, $p=0.030$) and OR 2.37 (95% CI 1.29 to 4.34, $p=0.005$)) respectively (Harrison et al., 2014) [evidence level III-2].

The prevalence of severe homozygous (ZZ) α_1 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 α_1 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 α_1 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 comorbidity. (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[‡] by their respiratory physician owing to their long-standing relationship with the clinician. Terminal care does not always require specialist palliative care unless there are problems with symptom control or other complex needs. Hospice or specialist consultations should be available to patients should they be required.

[‡] Terminal Phase is characterised by the following criteria:

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

O1. Inhaled bronchodilators

Inhaled bronchodilators provide symptom relief and may increase exercise capacity(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 beta₂-agonists (SABA)

Regular short-acting beta₂-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 FEV₁ 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 beta₂-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 muscarinic antagonist (SAMA)

The duration of action of short-acting muscarinic antagonists (formerly known as anticholinergics) is greater than short-acting beta₂-agonists. A systematic review of randomised controlled trials comparing ipratropium bromide alone, or in combination with short-acting beta₂-agonists, against short-acting beta₂-agonists alone found significant benefits for regimens containing ipratropium bromide.(Appleton et al., 2006a) Ipratropium bromide improved spirometry over short-acting beta₂-agonists alone, weighted mean difference = 30mls (95% CI 0 to 60) for FEV₁ 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 beta₂-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 FEV₁ 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 beta₂-agonists or ipratropium bromide, significantly increase lung function measurements in COPD. Ipratropium bromide has a significantly greater effect on lung function compared to beta₂-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([Braido 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 muscarinic antagonists (LAMA)

Long-acting muscarinic antagonists (formerly known as anticholinergics) e.g. tiotropium, glycopyrronium bromide and umeclidinium cause bronchodilation with a duration of action of over 24 hours and are used once daily. ([Maltais et al., 2011](#), [Trivedi et al., 2014](#)) Acclidinium bromide is another long-acting muscarinic antagonist used twice daily. ([Karabis et al., 2013](#)) A systematic review ([Karner et al., 2014](#)) 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 FEV₁ 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 ([Karner et al., 2014](#)). Refer Section P5.1 for further information on tiotropium mortality. Systematic reviews ([Barr et al., 2006](#)),([Barr et al., 2005](#)) found tiotropium produced a significant increase in FEV₁ 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 beta₂-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 FEV₁ 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 FEV₁ = 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 FEV₁) were enrolled in these trials which assessed overall death and cardiovascular death. 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 regarding 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 5ug or via Handihaler 18ug there was no increased risk of death in either of the two Respimat arms compared with the Handihaler arm [HR for Respimat 5 ug v Handihaler was 0.96 (95% CI 0.84-1.09); for Respimat 2.5ug 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 5ug 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 (5ug).

Glycopyrronium bromide (NVA237) is another inhaled, once daily, long-acting muscarinic antagonist. 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 FEV₁, 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 regards to spirometry, quality of life and moderate to severe exacerbations(Kerwin et al., 2012) [evidence level II].

Acclidinium is a long-acting muscarinic antagonist used twice daily. Two randomised controlled trials of 12 to 24 weeks duration have demonstrated improved bronchodilation (trough and peak FEV₁), quality of life (SGRQ) and dyspnoea (TDI) with acclidinium, compared with placebo(Kerwin et al., 2012, Jones et al., 2012) [evidence level II].

01.2.2 Long-acting beta₂-agonists (LABA)

Long-acting beta₂-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., 2006d) found that compared to placebo, long-acting beta₂-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 beta₂-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], FEV₁ 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 et al., 2013). Olodaterol is another once daily long- acting beta₂-agonist which improves FEV₁ and reduces rescue inhaler use compared with placebo. It appears to be generally safe (although generally asymptomatic increases in plasma creatinine phosphokinase have been reported) and to have similar bronchodilator effects to BD formoterol. (Ferguson et al., 2014, Koch et al., 2014) [evidence level II]

The efficacy of long-acting beta₂-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 FEV₁, 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 (LAMA / LABA)

A Cochrane systematic review of five studies found that the combination of tiotropium and a long-acting beta₂-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 FEV₁ 0.07 L; 95% CI 0.05 to 0.09), compared to tiotropium alone (Karner 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 FEV₁ (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]. Overall, these benefits of indacaterol/glycopyrronium were supported by systematic reviews (Ulrik, 2014, Rodrigo and Plaza, 2014) [evidence level I]

Once-daily UMEC/VI 62.5/25 mcg was well tolerated and provided clinically-significant improvements in lung function and symptoms compared with placebo in patients with COPD (Donohue et al., 2013, Donohue et al., 2014) [evidence level II]. Combination treatment with once-daily umeclidinium plus vilanterol improved lung function compared with tiotropium monotherapy in patients with moderate to very severe COPD. All treatments had a similar safety profile. There were no significant differences between treatment groups with respect to risk of COPD exacerbation, transition dyspnoea index (TDI)

focal score; Shortness of Breath with Daily Activity (SOBDA) diary score or SGRQ scores(Decramer et al., 2014)[evidence level II].

O1.3 Assessment of response and continuation of bronchodilator therapy

In some patients a response to bronchodilator therapy may require treatment for up to two months. Symptomatic and functional benefits can often be demonstrated in the absence of an increase in FEV₁. 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).

O2. Oral bronchodilators

O2.1 Methylxanthines

Theophylline has a modest effect on FEV₁ 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 FEV₁, 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 FEV₁ 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 (ICS)

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 FEV₁ (**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]. The 12 month Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial, studied patients with severe COPD who were stable on triple therapy (tiotropium, fluticasone propionate and salmeterol). Staged withdrawal of fluticasone propionate over 12 weeks was compared to continuation of fluticasone propionate, plus salmeterol and tiotropium (Magnussen et al., 2014). 2495 COPD patients with FEV₁ <50% predicted and a history of at least one exacerbation in the last 12 months were studied. The hazard ratio for the first COPD exacerbation that was moderate or severe was 1.06 with ICS withdrawal (95% CI 0.94 to 1.19) which was below the upper limit of the non-inferiority margin for the primary outcomes of exacerbation of 1.20 [evidence level II]. The mean reduction in FEV₁ was 43ml greater in the ICS withdrawal group at 52 weeks, which was statistically significant. At 52 weeks there was no statistically different significance in a mMRC dyspnoea score, and there was a small difference in change in SGRQ score, favouring ICS continuation. Although the authors concluded that in patients with severe COPD withdrawal of ICS in a tapered fashion was non-inferior to continuation of ICS, there were statistically significant reductions in FEV₁ and quality of life which may be clinically relevant to some patients. Individual patient follow up is recommended if ICS is withdrawn.

O3.3 Inhaled corticosteroids versus long-acting beta₂-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 FEV₁ (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 beta₂-agonists in combination (ICS/LABA)

A systematic review of 19 randomised controlled trials involving 10,400 COPD patients of combined corticosteroids and long-acting beta₂-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 of 14 studies (Nannini et al., 2012) (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 FEV₁ 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 beta₂-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 flunisolide 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 FEV₁ <50% predicted.

Fluticasone furoate/vilanterol is a new once daily ICS/LABA combination inhaled medicine. In short term studies of 12 weeks duration, fluticasone furoate/vilanterol had comparable lung function and quality of life effects as fluticasone propionate/salmeterol twice daily (Agusti et al., 2014), (Dransfield et al., 2014). Longer term studies (6 months) have shown that fluticasone furoate/vilanterol improves lung function compared to fluticasone furoate alone or placebo, and was similar in effect to vilanterol (Kerwin et al., 2013), (Martinez et al., 2013). In a 12 month study of COPD patients with a history of exacerbations, fluticasone furoate/vilanterol reduced the rate of moderate to severe exacerbations by 20 to 30% compared to vilanterol alone, whereas the rate of pneumonia increased approximately 2-fold (Dransfield et al., 2013). The study reported event-based number needed to treat to prevent a moderate or severe exacerbation per year of 3.3 to 5.6 for the 3 doses of fluticasone furoate/vilanterol used, compared to vilanterol. In comparison, the event-based number needed to harm for pneumonia was 19 to 27 for fluticasone furoate/vilanterol, compared to vilanterol. 8 deaths from pneumonia were observed in the patients treated with fluticasone furoate/vilanterol (7 of whom were in the highest dose of 200/25 mcg), compared to no deaths from pneumonia in the vilanterol group. A higher number of fractures was observed in the fluticasone furoate/vilanterol groups. The study authors advised that clinicians should weigh up the benefit of reduced exacerbations with the risk of pneumonia when considering fluticasone furoate/vilanterol, and recommended that the 100/25 mcg dose be the maximum dose used in future clinical trials.

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 regarding the long-term benefits and risks of treatment with tiotropium in addition to inhaled corticosteroid and long-acting beta₂-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 FEV₁, the primary outcome, with triple therapy, mean difference pre-dosing 128 (95% CI 78, 179) mls. Similar effects on FEV₁ 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

O5.1 Inhaler technique

Inhaler devices must be explained and demonstrated for patients to achieve optimal benefit. It is necessary to check regularly that the patient has the correct inhaler technique. Elderly and frail

patients, especially those with cognitive deficits, may have difficulty with some devices. 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)

O5.2 Inhaler adherence

A systematic review comprising predominantly retrospective database studies which measured prescription refill adherence with one to two year follow-up of patients with COPD found increased hospitalizations, mortality, poor quality of life and loss of productivity among non-adherent patients (van Boven et al., 2014) [evidence level III-2].

The National Asthma Council of Australia's Australian Asthma Management Handbook contains further information about adherence: <http://www.astmahandbook.org.au/management/adherence>.

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 VO₂ 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_Imax) 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., 2010c). 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

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) There are few robust studies that have attempted to evaluate the role of disease specific education in addition to exercise training. An Australian multicentre RCT of 267 people with COPD failed to show any additional benefit with the combination of an 8-week pulmonary rehabilitation program comprising exercise training and disease specific education with a self-management focus, compared to exercise training alone. The outcomes assessed in this study included disease specific and generic HRQoL, functional exercise capacity, dyspnoea, health behaviours, self-efficacy and healthcare utilisation (respiratory-related hospital admissions, physician consultations and prescriptions)(Blackstock et al., 2014).

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. Refer to P1.1 for additional information regarding smoking cessation.

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 (Poulain 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 FEV₁, 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].

Omega-3 fatty acids: Omega-3 fatty acids have been demonstrated to have diverse anti-inflammatory effects. Two RCTs have examined the effect of omega-3 polyunsaturated fatty acids (PUFA) in COPD. One RCT randomised 32 COPD subjects to supplementation with 0.6g omega-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 omega-3PUFA/exercise group compared to controls. (Sugawara et al., 2010) The other study compared the effects of 8 weeks supplementation with 3g omega-3PUFA/day versus a placebo in 102 COPD subjects undergoing pulmonary rehabilitation. They reported an increase in exercise capacity in the omega-3PUFA group compared to the placebo group, but there were no effects on muscle strength, FEV₁ or inflammation. (Broekhuizen et al., 2005) Hence omega-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 FEV₁ 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 out-patients, 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(Laviolette 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 wholegrain varieties, such as breads, cereals, rice and pasta; lean meats and poultry, fish, eggs, 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 46metres 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. The concept of multimorbidity has been increasingly discussed in primary care. Multimorbidity refers to co-occurrence of two or more chronic medical conditions that may or may not directly interact with each other within the same individual. Multimorbidity is the norm rather than the exception in older primary care patients. (Mercer et al., 2009) Managing patients with multimorbidity effectively involves taking a patient-centred approach to balancing multiple, and at times competing, priorities. Some of the common comorbidities experienced by people with COPD (e.g. obesity, anxiety, depression, osteoporosis and metabolic disease) are associated with poorer physical performance as measured by the distance walked on the 6MWT (Li et al., 2014)

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). The most common comorbidities differ between men and women. Specifically women are more likely to demonstrate anxiety and depression than men. (Aryal et al., 2014)[evidence level III-2].

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 potential confounders. 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].

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 conditions 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 CV events (Hole et al., 1996), (Agarwal et al., 2012) [evidence level III-2]. Arterial stiffness has been proposed as one potential mechanism for this excess of CVD as it strongly predicts CVD events and mortality. In COPD, arterial stiffness increases during exacerbation and is associated with COPD severity (measured as airflow obstruction or degree of emphysema), inflammation, oxidative stress and sympathetic nervous system (SNS) tone. COPD also predicted lipid core (OR 2, CI 1.25-3.69, p=0.0058), plaque component vulnerable to rupture (Lahousse et al., 2013) [evidence level III-2], which increases risk of acute CVD events.

One review (Vivodtzev et al., 2014) [evidence III-2] demonstrates results across multiple studies showing increased arterial stiffness (n=18), endothelial dysfunction (n=4) and carotid intima-media thickness (n=3) in COPD. Several trials showed a graded effect, with an increase in COPD subjects compared with non-COPD smokers, and in smokers compared with healthy non-smokers. This group also summarised preliminary data suggesting that current therapeutic interventions may impact on increased arterial stiffness; included studies reported a statistically significant improvement in arterial stiffness after standard pulmonary rehabilitation, after treatment with combination inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) or long-acting antimuscarinic (LAMA), and possible improvement with supplemental oxygen.

Konecny's group sought to explore cardiac arrhythmia as a potential source of the excess CVD mortality in COPD in a retrospective record review of 7441 subjects who underwent 24 hour Holter monitoring and spirometry during the course of clinical assessment. The 3121 (49%) COPD patients demonstrated more arrhythmias than those without COPD; atrial fibrillation/flutter were identified in 23.3% versus 11% (p<0.0001), and non-sustained ventricular tachycardia in 13% versus 5.9% (p<0.0001). Both results remained statistically significant after adjustment for multiple confounders (Konecny et al., 2014) [evidence level III-2]. The study population was a highly select group, which potentially limits the broad application of the results. However, the study reports a "COPD dose effect", based on spirometry criteria, which adds weight to its conclusions.

Medications used in the treatment of COPD also have potential to impact on cardiac morbidity and mortality, due to intrinsic effects on chronotropy and muscle action potentials or due to side effects such as hypokalaemia. Medications implicated include beta-agonist and antimuscarinic bronchodilators and methylxanthines. More recently, macrolide antibiotics, which in chronic dosing have been shown to reduce respiratory exacerbations, have been added to the list, due to an association with QT

prolongation and bradycardia. Randomised controlled trials (RCT) of chronically dosed azithromycin have not demonstrated adverse cardiac effects in the clinical setting, particularly when known drug interactions are avoided. Likewise, for most inhaled bronchodilators, when used at therapeutic dose in stable COPD, there are no proven adverse effects on safety. Despite being common clinical practice, there is less evidence about the safety of high dose, combined bronchodilator therapy in the setting of acute exacerbation of COPD (AECOPD). 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 mortality predictors. 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].

Another prospective cohort study (Hoiseth et al., 2012) [evidence level III-2] reported results for 99 COPD patients with 217 exacerbations and a median follow up duration of 1.9 years and found NT-pro BNP to be an independent risk factor for mortality after AECOPD. Dividing NT-pro BNP levels into tertiles, mortality rates were 8.6, 35 and 62 per 100 patient years (age-adjusted log-rank $p < 0.0001$) and, compared to the lowest tertile, adjusted HR for death were 2.4 (CI 0.95-6.0) and 3.2 (CI 1.3-8.1) in the intermediate and highest tertiles, respectively.

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. In addition, Abusaid’s group (Abusaid et al., 2009) [evidence level III-2] proposed a contributory role for diastolic dysfunction (DD) in AECOPD. Their retrospective single centre cohort study reported that DD was associated with prolonged length of hospital stay (4.02 versus 3.24 days, $p = 0.005$) and increased frequency of hospitalisation for AECOPD (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 cardiac adverse events (CAE) associated with AECOPD. Using self-controlled case series methodology, they identified 25,857 COPD patients and their CAEs (524 myocardial infarctions (MI) 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 quality of life (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, two studies have looked at the impact of COPD on outcomes after first MI (Bursi et al., 2010), (Andell et al., 2014) [evidence level III-2]. Prevalence of clinically diagnosed COPD in these studies was 12% and 6%, respectively. In Bursi's American cohort, 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. Likewise, Andell's group reported worse outcomes for COPD patients in their Swedish cohort: one year mortality 1.14 (1.07 - 1.21), and development of heart failure 1.35 (1.24 - 1.47). Bursi's group found that the association of COPD with survival remained unchanged over time, despite an overall decline in mortality after MI (seen with improvements in medical care). The difference in clinical presentation and therapeutic interventions received reported by Andell's group, may partially explain the discrepant outcomes seen in COPD patients (COPD patients were more likely to present with atypical symptoms, less likely to undergo percutaneous revascularisation procedures or to receive secondary prevention medications).

07.2.1 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 of patients admitted with heart failure (Iversen et al., 2008) [evidence level III-2] 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%, $p = 0.03$). Potential mechanisms contributing to the high rates of heart failure in COPD include coronary artery disease (CAD), hyperinflation, sympathetic nervous system and renin-angiotensin system activation, pulmonary hypertension and right heart dysfunction.

Barr and colleagues investigated a subgroup from the Multi-ethnic Study of Atherosclerosis (MESA): a multi-centre, prospective, cross-sectional study of CVD. The group initially reported 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 magnetic resonance imaging (MRI) (Barr et al.) [evidence level III-2]. The same association was not present for left ventricular ejection fraction. Smoking status was an effect modifier, with a greater effect seen for current smokers. Similar relationships were obtained for measures of airflow obstruction. Subsequently, the group has explored mechanisms in a smaller subset of the MESA population, reporting that pulmonary vein area, assessed via cardiac MRI, was significantly less in COPD subjects than in non-COPD controls and inversely associated with percentage emphysema on CT chest (Smith et al., 2013) [evidence level III-2]. These results implicate upstream pulmonary factors, rather than intrinsic cardiac dysfunction, as the source of impaired left ventricular

filling and diastolic dysfunction in COPD.

In COPD, heart failure adversely impacts on morbidity and prognosis. A prospective cohort study (Boudestein et al., 2009) [evidence level III-2] further clarifies this relationship; Boudestein's group 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).

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.

07.2.2 Safety of beta-blockers

Beta-blockers have well established survival 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 FEV₁, increase in respiratory symptoms or change in the response to inhaled beta₂ 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. COPD symptoms are more pronounced during exertion and hence a recent study (Mainguy et al., 2012) [evidence level II] has investigated dynamic lung function in GOLD stage II-III COPD patients during cardioselective beta-blocker treatment. This randomised, double blinded, placebo-controlled cross over trial compared inspiratory capacity (IC) at peak isotime exercise during endurance exercise testing as a measure of dynamic hyperinflation for treatment arms with bisoprolol (titrated to 10 mg) and titrated placebo. Included patients had no recognised indication for beta-blocker treatment and were randomised to treatment sequence. As expected, IC reduced with exercise; this effect was more pronounced in the bisoprolol arm -0.50 versus -0.41 (p<0.01). Exercise duration was non-significantly reduced in the bisoprolol arm, and the change was strongly correlated with the change in IC. However, the absolute difference was modest and of arguable clinical significance and so the groups recommended that cardioselective beta-blockers not be withheld on this basis. Beta-blockers have duration-dependent effects, including effects on beta-receptor regulation, which are important in their efficacy for heart failure and may also be relevant in the airways. The 14 day beta-blocker treatment duration in this study was likely insufficient to fully demonstrate these effects.

A number of observational studies also lend confidence to beta-blocker prescribing in COPD patients. Six 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, Quint et al., 2013) [evidence level III-2]. Beta-blocker prescription rates for COPD subjects ranged from 17% - 77%. All studies reported significant reduction in mortality associated with beta-blocker use and adjusted potential confounders. Only Olenchock's group did not attempt additional adjustment for beta-blocker prescribing propensity.

Rutten's group in addition reported reduced AECOPD (HR 0.71, 95% CI 0.6 to 0.83). Importantly, in Short's study, beta-blockers did not worsen lung function decline in the 2712 subjects for who serial measures were available. In fact, beta-blockers were associated with reduced risk of oral corticosteroid courses and respiratory-related hospital admissions.

Quint's population-based cohort study utilised detailed hospital MI data linked to longitudinal primary care records to investigate MI mortality outcomes in COPD patients between 2003 and 2008. Of 39% prescribed beta-blocker medication during the index hospital admission, 79% remained on beta-blocker treatment for one year. Beta-blocker treatment was associated with survival benefit, whether prior treatment was continued (HR 0.59 (CI 0.44 - 0.79)) or newly commenced (HR 0.5 (CI 0.36 - 0.69)) during the index admission. However, 52% of 2209 eligible subjects were coded to beta-blocker status categories other than "yes" or "no" and excluded, with 59% of these allocated to the category "beta-blocker contraindicated" (for reasons not specified). This is a concern in terms of potential bias, despite the authors' efforts to address this.

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.

07.2.3 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. Systematic reviews and meta-analysis have suggested beneficial effects of statin treatment in COPD (Dobler et al., 2009, Janda et al., 2009, Horita et al., 2014). Horita's group performed meta-analysis for mortality outcomes in 10 cohort studies and reported a protective effect: HR 0.81 (0.75 - 0.86). Sensitivity analyses using subgroups and alternative modelling remained statistically significant, although the included studies were heterogeneous and publication bias was likely.

A prospective multicentre RCT explored the role of long-term simvastatin treatment (40mg/day) in AECOPD prevention in moderately severe COPD patients, who did not have any conventional indication for statin treatment (Criner et al., 2014) [evidence level II]. The study was stopped prematurely, prior to attaining recruitment targets, due to futility. Whilst simvastatin treatment resulted in the expected improvements in dyslipidaemia, two consecutive interim analyses showed no beneficial effect on exacerbation rates or time to exacerbation in the study population as a whole, or in any subgroup.

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 FEV₁, 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) 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.

07.4 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 β -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_2 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_2 <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.

07.5 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 disease (GORD)

In patients with COPD, hyperinflation, coughing and the increased negative intrathoracic pressures of inspiration may predispose to reflux, especially during recumbency and sleep. Microaspiration of oesophageal secretions (possible including refluxed gastric content) is a risk, especially with coexistent snoring or OSA. Reflux and microaspiration exacerbate cough, bronchial inflammation and airway narrowing. A nested case control study performed on a large primary care dataset found a modest increased risk 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](#)) although higher relative risks have been reported in other studies and Sakae et al reported a RR of 13.06 (95% CI 3.64-46.87) in their systematic review and meta-analysis of exacerbations of COPD and symptoms of GORD. In a large cross-sectional study of patients with a wide range of COPD severity, forming part of the US COPD Gene Study, 29% of patients reported a diagnosis of physician-diagnosed GORD([Martinez et al., 2014](#)). In this study, GORD symptoms were associated with worse health related quality of life (HRQOL) (SGRQ), increased dyspnoea and more frequent exacerbations. Two of these three associations persisted after adjusting for the use of proton pump inhibitors (PPI) (although the latter was associated with an improvement in HRQOL). It is noted that PPI use in the general population is associated with a higher frequency of pneumonia (([Gulmez et al., 2007](#), [Eurich et al., 2010](#))). Nonetheless, other studies have suggested PPI use is associated with a reduction in exacerbations in GORD-sufferers([Sakae et al., 2013](#), [Sasaki et al., 2009](#)) . In the study by Martinez et al, subjects with GORD were more likely to be female, to have symptoms of chronic bronchitis and to have a higher prevalence of cardiovascular disease. Over two years of follow-up the presence of GORD symptoms was associated with more frequent exacerbations which association was not altered by PPI use. In another prospective cohort study, gastro-oesophageal reflux symptoms were associated with an increased risk of exacerbation([Terada et al., 2008](#)).

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

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)

07.8 Alcohol and sedatives

Patients with COPD have impaired gas exchange and an exaggerated fall in PO_2 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.

07.9 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.

07.10 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 population cohort of community dwelling elderly (age 70-89) with normal cognition, those who had a diagnosis of COPD at baseline (based on medical record data), had an 83% increased risk of incident non-amnesic mild cognitive impairment (hazard ratio 1.83, 95%CI 1.04-3.23) over 5 years(Singh et al., 2014). Cognitive function in patients admitted to hospital with acute exacerbation of COPD was more impaired than in patients with stable COPD which in turn was worse than in a matched control group(Dodd et al., 2013) [evidence level III-2].

In a meta-analysis of 655 patients with stable 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 PaO₂ less than or equal to 55mmHg or
- Arterial PaO₂ 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 (FEV₁ 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 PaO₂ and mean PAP although FEV₁, Pulmonary Capillary Wedge Pressure and D_LCO were correlated in a multiple regression model. In those COPD patients with severe PHT, hypoxaemia, reduced D_LCO 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].

Retrospective data from 60 patients with severe COPD who had undergone CT chest, transthoracic echocardiography and right heart catheterisation showed that a CT chest pulmonary artery to aorta ratio greater than one was 73% sensitive and 84% specific for pulmonary hypertension with right

heart catheter as the gold standard. This was significantly more sensitive and specific than transthoracic echocardiography, (Iyer et al., 2014)[evidence level IV].

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 transoesophageal 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]. This meta-analysis included data from 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). McEvoy et al found a small mortality benefit in the NIV group, at the expense of worse quality of life(McEvoy et al., 2009)[evidence level II]. Mean pressures used were IPAP 13cmH₂O, EPAP5cmH₂O. No significant reduction in PaCO₂ was observed.

In 2014 two further randomised controlled trials of long term NIV in patients with COPD were published. A major difference from the McEvoy trial is the significantly higher inspiratory positive pressures used. Kohnlein et al (Kohnlein et al., 2014) randomised 195 patients with clinically stable, severe COPD and hypercapnia to NIV or usual care. Both groups were admitted to hospital every 3 months for 1 year for 'treatment optimisation'. NIV was titrated to target a reduction in PaCO₂ by 20% or achieve PaCO₂ of less than 48mmHg. There was a significant reduction in 1-year mortality. 12% mortality in the intervention group and 33% in the control group was reported; hazard ratio 0.24 (95% CI 0.11–0.49; p=0.0004) [evidence level II]. Mean pressures used were IPAP 22cmH₂O, EPAP 5cmH₂O. Mean reduction in PaCO₂ was 7mmHg. In direct contrast to this finding, Struik et al 2014 found no mortality or exacerbation rate difference in a 12 month randomised controlled trial (n =201) of NIV and usual care in patients with severe COPD who had been admitted to hospital with an exacerbation of COPD and hypercapnia (Struik et al., 2014). Mean pressures used were IPAP 19cmH₂O, EPAP 5cmH₂O. Mean reduction in PaCO₂ was 3.8mmHg.

Comparison between the three trials above is difficult as they have used different treatment algorithms and NIV pressure settings. Furthermore, inclusion criteria and patient characteristics also differed significantly. For example, McEvoy et al performed a baseline diagnostic sleep study and excluded patients with OSA. A baseline PSG was not performed in the other trials. It is also unclear if the results from the Kohnlein trial are generalizable to an Australasian patient population given that all subjects were electively admitted 3 monthly. With such significant heterogeneity of results, patient characteristics and methodology, it remains unclear if long term NIV should be recommended for patients with severe stable COPD and hypercapnia. Referral for specialist opinion at an institution with expertise in this area should be sought.

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 and other techniques

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(Shah and Herth, 2014). Deslee reports on a multicentre cohort study of 60 highly selected severe COPD patients receiving bronchoscopic lung volume reduction with nitinol coil deployment. Six month follow up data shows modest benefits in quality of life, dyspnoea and lung function ((Deslee et al., 2014). Prospective randomised controlled trials are needed before any recommendations can be made.

09.3 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. 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 $\text{D}_\text{LCO} < 20\%$ 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

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 begin the discussion with patients about the course of their disease. Consideration should be given to appointing an Enduring Power of Attorney (EPOA) for financial matters, as well as an EPOA for medical management. There are multiple online resources, e.g. from the Office of the Public Advocate in Victoria: <http://www.publicadvocate.vic.gov.au/>, but these are also available through any solicitor or legal 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 legal documents. They are of course useless residing in a drawer at the patient's home unknown to those who can enact their directives. The discussion about pros and cons of intubation and easy vs. difficult weaning from intubation (including the concept of tracheostomy) may need input from a respiratory physician, but it is ultimately up to the patient's general practitioner to begin the discussion and not leave it too late in the patient's disease course.

A useful resource to guide patients in making these choices is 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 FEV₁ in people who continued to smoke compared to those who ceased (Lee and Fry, 2010) [evidence level I]. The annual decline in FEV₁ 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 FEV₁ 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]

A comprehensive review of smoking cessation in patients with respiratory diseases has been published by the European Respiratory Society (www.ersnet.org/ers/lr/browse/viewPDF.aspx?id_attach=17030) (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 (Cahill et al., 2013) Behavioural techniques further increase the quit rate. (Eisenberg et al., 2008, Hartmann-Boyce et al., 2014, Stead et al., 2013c) (Civljak et al., 2013) (Stead et al., 2013a) (Whittaker et al., 2012, Cahill et al., 2010), (Stead and Lancaster, 2005), (Lancaster and Stead, 2005) [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 and in pregnant women (NHLBI/WHO Workshop Report, April 2001) International data show that smoking cessation strategies are cost effective but with a 10-fold range in cost per life-year gained depending on the intensity of the program and the use of pharmacological therapies (NHLBI/WHO Workshop Report, April 2001). A range of health professionals can help smokers quit (Rice et al., 2013), (Stead et al., 2013a), (Carr and Ebbert, 2012), (Sinclair et al., 2004) 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) Comprehensive treatment of tobacco dependence involves providing both behavioural support and pharmacotherapy. (Zwar et al., 2014) A systematic review of behavior change techniques to support smoking cessation in patients with COPD found that four techniques were associated with higher rates of cessation. The behaviour change techniques found to be effective (usually in comparison to usual care) were; facilitate action

planning/develop treatment plan, prompt self-recording, advise on methods of weight control, and advise on/facilitate use of social support. In addition linking COPD and smoking was found to result in significantly larger effect sizes (Bartlett et al., 2014) [evidence level 1]. Personalising smoking cessation advice based on lung function results increase cessation rates. (Parkes et al., 2008) [evidence level 1] Currently accepted best practice is summarised in the 5-A strategy: (Zwar et al., 2014)

- Ask and identify smokers. Document smoking status in the medical record.
- Assess the degree of nicotine dependence and motivation or readiness to quit
- Advise smokers about the risks of smoking and benefits of quitting and discuss options
- Assist cessation — this may include specific advice about pharmacological interventions or referral to a formal cessation program such as the Quitline
- 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 *possibly relapsing (maintenance)* before achieving long-term success. People at all stages can be offered assistance but advice tailored on the basis of the patient's readiness to quit. (Zwar N, 2004) Brief interventions for smoking cessation involve opportunistic advice, encouragement and referral. Referral options are the Quitline (13 7848) and an accredited tobacco treatment specialist (aascp.org.au). Cessation rates increase with the amount of support and intervention, including practical counselling and social support arranged outside of treatment.

Smoking tobacco can alter the metabolism of a number of medicines. This is primarily due to substances in tobacco smoke, such as hydrocarbons or tar-like products that cause induction of some liver enzymes (CYP 1A2, in particular). When a person stops smoking, the enzyme activity returns to normal, which may result in increased levels of these medicines in the blood. Monitoring and dosage reduction may often be required. For information on medicines affected by smoking see appendix 3 of the RACGP smoking cessation guidelines (<http://www.racgp.org.au/your-practice/guidelines/smoking-cessation/>).

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 offered to all nicotine dependent smokers who express an interest in quitting, except when contraindicated (NHLBI/WHO Workshop Report (April 2001), (2008) [evidence level I]. Caution is recommended in people with medical contraindications, pregnant women and adolescent smokers. (NHLBI/WHO Workshop Report, April 2001) Nicotine patches, varenicline and bupropion sustained release are all PBS listed for smoking cessation. Details of PBS listing are available in the RACGP smoking cessation guidelines (<http://www.racgp.org.au/your-practice/guidelines/smoking-cessation/>) and the Australian Medicines Handbook (<https://shop.amh.net.au/>).

A Cochrane network analysis concluded that combination NRT (nicotine patch combined with a quick-acting oral form) and varenicline (used as monotherapy) are the most effective forms of drug treatment and work equally well. It has been shown that varenicline is more effective than bupropion in a number of studies. Head to head comparisons between bupropion and NRT monotherapy have shown these medicines are equivalent to each other in efficacy. (Cahill et al., 2013)

P1.2.1 Nicotine replacement therapy

All forms of nicotine replacement therapy (NRT) appear to be useful in aiding smoking cessation and increase the rate of quitting by 50-70%. (Stead et al., 2008) [evidence level 1] NRT is most suitable for nicotine dependent smokers who are motivated to quit. All forms of NRT (at equivalent doses) are similarly effective in aiding long-term cessation. Evidence for efficacy of NRT is strongest in those who smoke more than 15 cigarettes daily but there is also evidence of benefit in lighter smokers who choose to use pharmacotherapy (Shiffman, 2005) [evidence level II]. There are a range of forms available in Australia (transdermal patch, gum, inhaler, inhalator, lozenge, mouth spray and oral strip). 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). All forms of NRT should be used for at least eight weeks. Up to date information on the forms of NRT available, PBS listing and initial dosing guidelines are available in the RACGP smoking cessation guidelines (<http://www.racgp.org.au/your-practice/guidelines/smoking-cessation/>) and the Australian Medicines Handbook (<https://shop.amh.net.au/>).

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]. NRT should be used with caution in people with recent myocardial infarction, unstable angina, severe arrhythmias and recent cerebrovascular events (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.

Combination NRT. Combining two forms of NRT (patch plus oral form, such as gum or lozenge) has been shown to be more efficacious than a single form of nicotine replacement. The patch provides a steady background nicotine level and the oral forms provide relief for breakthrough cravings as needed. There is evidence from nine trials that this type of combination NRT is more effective than a single type (Stead et al., 2012) [evidence level 1]. Health professionals should encourage smokers to use combined NRT if they are unable to quit using one NRT product alone, or experience cravings using only one form of NRT. Combination NRT can also be recommended as first line treatment.

Pre-cessation nicotine patch. There is evidence to support use of the nicotine patch prior to smoking cessation. A meta-analysis found that the nicotine patch used prior to quit day increased success rates compared to standard therapy. (Shiffman and Ferguson, 2008) [evidence level 1]

Reduce to quit. There is also evidence for use of NRT to help smokers who are not willing to quit immediately to reduce their tobacco and then progress to quitting. A meta-analysis found that reducing cigarettes smoked before quit day versus quitting abruptly, with no prior reduction, produced comparable quit rates. (Lindson et al., 2010)

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., 2014). This review included a total of 90 trials, 44 of which assessed the effect of bupropion and ten nortriptyline. Pooling six available trials using nortriptyline as the only pharmacotherapy showed evidence of a significant benefit for over placebo in achieving cessation in the longer (6-12 months) term (NNT = 10, 95% CI 6 to 21). 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 ≥ 6 months (44 trials, NNT = 16, 95% CI 13 to 20).). 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. As a result it is contraindicated in patients with past seizures, known CNS tumours, bulimia, alcohol abuse or a history of head trauma. Bupropion may interact with other antidepressants, especially monoamine oxidase inhibitors, which require a 14-day washout. 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. It is recommended as first-line pharmacotherapy for smoking cessation alongside NRT [evidence level 1], (NHLBI/WHO Workshop Report, April 2001) and is of similar efficacy as NRT monotherapy (Cahill et al., 2013). 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. Pooled results from four trials comparing bupropion to varenicline showed significantly lower quitting with bupropion than with varenicline (RR 0.68, 95% CI 0.56 to 0.83). 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 four trials of selective serotonin reuptake inhibitors or their own (two of fluoxetine, one of sertraline and one of paroxetine) and two trials of fluoxetine as an adjunct to NRT.. 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. Two trials of the herbal therapy St John's Wort also showed no benefit..

P1.2.3 Nicotine receptor partial agonists

The addictive properties of nicotine are considered to be mediated through its action as an agonist at $\alpha 4\beta 2$ nAChRs, 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. 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 ($n = 1,622$, $NNT = 14$, 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)

Cytisine, a naturally occurring substance chemically related to varenicline, has been used for smoking cessation for decades in parts of Eastern Europe. In the Cochrane meta-analysis of trials comparing cytisine with placebo, the risk ratio for cessation was 3.98 (95% confidence interval 2.01 to 7.87). Cytisine is not currently registered for use in Australia or New Zealand.

P1.2.4 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 ($NNT = 12$, 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)

P1.2.5 Electronic cigarettes (e-cigarettes)

E-cigarettes are battery-powered devices that may deliver nicotine in a vapour without tobacco or smoke. Before these products can be recommended for consumers, further research must be conducted on their safety and efficacy for smoking cessation. E-cigarettes can relieve cravings and symptoms of nicotine withdrawal as well as simulating the behavioural and sensory aspects of smoking. A small number of randomised controlled trials have suggested that e-cigarettes could have a role in cessation and harm reduction. A study in New Zealand found they had similar effects on six month cessation rates to nicotine patch among smokers wanting to quit (7.3% for e-cigarettes compared to 5.8% for patch) and rates were higher than for the participants randomised to non-nicotine containing e-cigarettes (3.6%). With such a large variety of e-cigarette products on the market and little data on their nicotine delivery, it is not known if their results can be generalised and further research is needed before recommendations for their use can be confidently made (Bullen et al., 2013) (Caponnetto et al., 2013). Concerns about e-cigarettes include a lack of evidence for short-term efficacy and short-and long-term safety, particularly in patients with current chronic disease. Rather than cessation, concurrent use with smoking may continue. A third of the participants allocated to e-cigarettes in a clinical trial reported continued product use at 6 months, suggesting that they might have become long-term e-cigarette users (Bullen et al., 2013). There are also concerns that e-cigarettes may potentially act as a gateway to smoking (Pepper and Brewer, 2014). As stated in the e cigarettes position paper from the Forum of Respiratory Societies, since electronic cigarettes generate less tar and carcinogens than combustible cigarettes, use of electronic cigarettes may cause less disease related to these components. However, the health risks of electronic cigarettes have not been adequately studied.

Refer to the following web links for further information: <http://www.firsnet.org/news-and-actions/30-firs-position-statement-on-e-cigarettes-launched-in-new-york-in-association-with-the-un-meeting-on-noncommunicable-diseases>

Therapeutic Goods Administration provides information: <https://www.tga.gov.au/community-ga/electronic-cigarettes>

Lung Foundation Australia has a position statement about electronic cigarettes: <http://lungfoundation.com.au/wp-content/uploads/2014/05/Lung-Foundation-Australia-E-Cigarettes-Position-Statement-18-June-2014.pdf>

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 routine 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, antibiotics should be used in exacerbations with clinical signs of infection (increased sputum purulence in addition to increased breathlessness, cough and/or increased sputum volume (see Section X).

For patients with moderate-severe COPD and recurrent exacerbations, recent trials have found that long-term low-dose oral macrolides reduce the number of patients experiencing an exacerbation and the frequency of exacerbations. The number needed to treat to prevent one exacerbation (NNT) was 8 (95% CI 5 to 18). (Herath and Poole, 2013) 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. It is not clear from the studies published in the Cochrane review to what extent participants had other treatment for their COPD maximised. However, prudence would suggest this treatment should be reserved for patients who have severe disease with recurrent exacerbations, in whom other treatments (for example: smoking cessation, pulmonary rehabilitation, vaccination and optimal use of other preventive pharmacotherapy known to reduce exacerbations) have been

optimised. Retrospective analysis of the trial by Albert et al found no evidence of treatment benefit among current smokers, with the greatest benefit seen in milder COPD and older subjects (Han et al., 2014). Prospective data in predefined groups is required before any sub-group treatment recommendations can be made.

Given the potential significant adverse effects of such regimens (including cardiac toxicity, ototoxicity, diarrhoea, and the development of antibiotic resistance [which affects both the individual and the community]), expert advice is recommended before starting long-term antibiotic therapy.

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 FEV₁ in patients with GOLD II COPD (43mls/year versus 49ml/year, p=0.024). However, the of pre-bronchodilator FEV₁ 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 regimes significantly reduced the odds of exacerbation compared with placebo - no single inhaled medication was more effective than another. If FEV₁ 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 FEV₁ 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 (FEV1 <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].

There is evidence to support the use of high dose oral N-Acetylcysteine in the reduction of COPD exacerbations and improvements in lung function. A large RCT involving 1006 Chinese patients with moderate to severe COPD evaluated the effect of high dose (600mg bd) N-acetylcysteine for a one year duration on acute exacerbations of COPD. They reported a significant reduction in acute exacerbations in the intervention group (1.16 exacerbations per patient-year) compared to placebo (1.49 exacerbations per patient-year; risk ratio 0.78, 95% CI 0.67–0.90; p=0.0011) (Zheng et al., 2014) [evidence level II]. In another RCT evaluating high dose N-Acetylcysteine (600mg bd) compared to placebo in 120 Chinese patients, there were significant improvements in the primary outcomes of FEF25-75 and in forced oscillation technique parameters at one year. (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 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, Tarpy 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, Tarpy 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), (Tarpy 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 PaO_2 consistently $< 55 \text{ mmHg}$ (7.3 kPa ; 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 $> 170 \text{ g/L}$), 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_2 is $55\text{--}59 \text{ mmHg}$ ($7.3\text{--}7.9 \text{ kPa}$; $\text{SpO}_2 < 90\%$). (Siafakas et al., 1995), (American Thoracic Society, 1995) Continuous oxygen therapy is of most benefit for patients with increased arterial PaCO_2 ($> 45 \text{ mmHg}$, 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 destaurate 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_2 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_2 during air travel should be maintained at more than 50 mmHg (6.7 kPa). At altitude, PaO_2 can be estimated from PaO_2 at sea level by means of published nomograms. If the PaO_2 at sea level is less than 70 mmHg (9.3 kPa), PaO_2 at 2300 metres is less than 50 mmHg (6.7 kPa). The natural conclusion is that all patients with a PaO_2 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 $\text{SpO}_2 \geq 90\%$ 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 a plan of care

COPD imposes handicaps which affect both patients and carers(Celli, 1995, Fishman, 1994),(Sprit 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(Kruis 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.

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., 2010c). 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, CO₂ 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 co morbidities.

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. Telehealth

Telemonitoring interventions ranging from simple telephone follow-up to daily telemonitoring of physiological or symptom scores, to more complex telemonitoring interventions with greatly enhanced clinical support; have been evaluated in patients with COPD. A Cochrane Review found that telehealth 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]. The positive effect of telemonitoring seen in some trials could thus be due to enhancement of the underpinning clinical service rather than to the telemonitoring communication.

Pinnock et al separated the effects of telemonitoring from the effects of existing services by adding telemonitoring alone to background self-management and clinical support in the usual care group. Adults registered with general practices in Scotland who had been admitted to hospital with an exacerbation of COPD in the previous year and who were thus at risk of future admissions were randomised to telemonitoring or usual care. All participants received self-management advice—education on self-management of exacerbations reinforced with a booklet, a written management plan, and an emergency supply of antibiotics and steroids, integrated within the standard clinical care service for the region. The telemonitoring package consisted of touch screen operated daily questionnaires about symptoms and drug use, with an instrument to measure oxygen saturation. Data were transmitted daily by an internet connection to the clinical monitoring team, which contacted patients whose score reached a validated threshold. Algorithms, based on the symptom score, alerted the clinical monitoring team if daily readings had not been submitted or if a high symptom score had

been recorded. Clinicians responded by advising rescue drugs, a home visit, admission to hospital, or further review. Intervention fidelity was high. After 12 months, no difference was seen in hospital admissions for COPD between the two groups (hazard ratio 0.98, 95% confidence interval 0.66 to 1.44). Furthermore, no differences were seen in health related quality of life, anxiety or depression, self-efficacy, knowledge, or adherence to drugs. This trial suggested that the addition of telemonitoring to the management of high risk patients, over and above the backdrop of self-management education and a good clinical service, is costly and ineffective (Pinnock et al., 2013) [evidence level II]. These findings are in agreement with a 2011 systematic review of telemonitoring, which suggested that in the absence of other care packages the benefit of telemonitoring is not yet proven and that further work is required before its wide-scale implementation.(Bolton et al., 2011)

D5. 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., 2010c) 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., 2010c), 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). A record linkage study in Canada found that elderly COPD patients prescribed benzodiazepines were at increased risk of an outpatient exacerbation (NNH 66, 95% CI 57–79) or an emergency department visit for COPD or pneumonia (NNH 147, 95% CI 123–181). There was also a slightly elevated albeit not significant risk of hospital admission (Vozoris et al., 2014) [Evidence Level III-2].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., 2010c).

D6. 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 8**.

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>).

D7. End-of-life issues

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

Determining prognosis in end-stage COPD is difficult, although guides to shortened survival include an $FEV_1 < 25\%$ predicted, weight loss (body mass index below 18), respiratory failure ($PaCO_2 > 50\text{mmHg}$, 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)

D7.1 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 beta₂ 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 PM10, black smoke and NO2 (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).

Statins have been shown to reduce rates of hospitalization (for COPD or any other reason), lung-function decline, the need for mechanical ventilation, and all-cause mortality in observational studies of COPD patients. The Prospective Randomized Placebo-Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations (STATCOPE) examined the effect of daily treatment with simvastatin in patients with moderate-to-severe COPD who were at high risk for exacerbations and had no other indications for statin treatment. Simvastatin at a daily dose of 40 mg for at least 12 months did not affect exacerbation rates or the time to a first exacerbation (Criner et al., 2014) [evidence level II].

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 FEV₁ manoeuvre. An FEV₁ 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 FEV₁ 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 PaO₂ less than 60 mmHg (8 kPa) indicates respiratory failure, while a PaCO₂ greater than 45 mmHg indicates ventilatory failure. Respiratory acidosis indicates acute respiratory failure warranting consideration for assisted ventilation.

Chest x-ray and electrocardiogram: These help to identify alternative diagnoses and complications, such as pulmonary oedema, pneumothorax, pneumonia, empyema, arrhythmias, myocardial ischaemia and others.

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 re-admission (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% (PaO₂ > 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

Walters et al report that there is high-quality evidence that systemic corticosteroids reduce treatment failure (defined as additional treatment, hospital admission/re-admission for index episode, return to emergency department, unscheduled physician visit for the index episode), improve lung function, shorten recovery and reduce the severity of acute exacerbations of COPD (Walters et al., 2014a) [evidence level 1]. Systemic corticosteroids reduced the risk of treatment failure by over half compared with placebo in nine studies (n = 917) with median treatment duration 14 days, odds ratio (OR) 0.48 (95% confidence interval (CI) 0.35 to 0.67. The number needed to treat to avoid one treatment failure is 9. There is no evidence that treatment with corticosteroids alters mortality.

Unlike earlier reviews this review included four papers that compared intravenous corticosteroids with oral corticosteroids and two papers with ventilated patients in ICU. In patients requiring ventilation in ICU, pooled data did not show a reduction in length of stay, duration of ventilation or mortality in those receiving corticosteroids compared with placebo. Walters et al concluded that there is no evidence of benefit for intravenous treatment compared with oral treatment with corticosteroids on treatment failure, relapse or mortality. Hyperglycaemia rates were higher with intravenous corticosteroids.

With regards to duration of treatment, a meta-analysis by Walters et al (Walters et al., 2014b) concluded that a shorter course of corticosteroids (around 5 days) is unlikely to lead to worse outcomes compared with a longer course. In 2013, Leuppi et al (Leuppi et al., 2013) reported on

the largest randomised controlled trial in this area. The authors 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) regarding subsequent exacerbations and mortality over six months of follow-up.

In light of the evidence above, it would appear that a 5 day course of oral prednisolone of 30mg to 50mg is adequate. In patients who have been on oral corticosteroids for longer than 14 days, tapering may be necessary. Patients on long-term oral corticosteroid therapy (> 7.5 mg prednisolone daily for more than 6 months) are at risk of developing osteoporosis. Prevention and treatment of corticosteroid-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 (FEV₁ < 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; I² = 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; I² = 33%). A re-examination of data from the placebo arm of a Spanish antibiotic trial that recruited patients with mild to moderate COPD from primary care confirmed that sputum purulence increased the likelihood of treatment failure 6 fold. A CRP elevated greater than 40 mg/L was also independently associated with a 13 fold increase in the risk of treatment failure. (Miravittles et al., 2013) [evidence level III-2].

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 amoxycillin (alternatively, erythromycin or roxithromycin). If patients do not respond, or if resistant organisms are suspected, amoxycillin-clavulanate should be prescribed. If

pneumonia, pseudomonas or staphylococci is suspected, appropriate antibiotics should be used.

Typically, a course of treatment should be over seven to 10 days. A response is usually seen within three to five days, and a change of antibiotic should be considered if the response is unsatisfactory. If parenteral administration was commenced, oral treatment should be substituted within 72 hours. 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 ($\text{PaCO}_2 > 70 \text{ mmHg}$), 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, McDonald et al., 2005)

Correction of hypoxaemia to achieve a 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 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 ($\text{NNH}=14$) (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_2 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 ($\text{PaO}_2 < 60 \text{ mmHg}$, 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 FEV₁ 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 (SpO₂ 88%–92%).
- **Respiratory function testing:** FEV₁ 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 11: 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 12**). 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 12: Follow-up – initial and subsequent

- Assessment of the patient's coping ability and strategies
- Measurement of FEV₁ 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	beta-agonist			
Improved exercise capacity				
Reduced breathlessness				
Improved quality of life				
	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
	Antimuscarinic (Anticholinergic)			
	Ipratropium	40-80mcg	6-8-hourly	MDI/spacer
	Tiotropium	18mcg	24-hourly	DPI
	Corticosteroid			
	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
<u>Metered dose inhaler (MDI)</u>	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)	MDIs should be used with a spacer device, as some people have difficulty coordinating the release of medication with inhalation.
<u>Spacers</u>	Aerochamber Breath-A-Tech Fisonair Nebuhaler Volumatic	- The spacer chamber acts as a reservoir for the aerosol released from an MDI. The patient can then inhale from this chamber without having to coordinate the release of the medication. - Use of spacers with inhaled corticosteroids reduces adverse effects of oral candidiasis and hoarseness, as well as optimising medication delivery. - MDI with spacer is as effective as a nebuliser if an equivalent dose is taken; 10-15 puffs of 100mcg salbutamol MDI via a spacer is therapeutically equivalent to a 5mg salbutamol nebule. - Spacers are cheap, portable, easily cleaned and maintained, do not require electricity and are simple and quick to use. - A small volume spacer is preferable when the vital capacity is less than 1.5L.
<u>Autohaler</u>	Airomir (salbutamol 100mcg); Qvar (beclomethasone 50mcg, 100mcg)	- Breath-activated MDI containing 200 doses of medication. - Use can improve lung deposition in patients with poor MDI inhaler technique. As the patient starts a slow, deep breath through the mouthpiece, a flap valve is triggered and the dose automatically releases.
Dry powder inhalers (DPI)		
<u>Accuhaler</u>	Serevent (salmeterol 50mcg); Flixotide (fluticasone 100mcg, 250mcg, 500mcg); Seretide (salmeterol 50mcg and fluticasone 100mcg, salmeterol 50mcg and fluticasone 250mcg, salmeterol 50mcg and fluticasone 500mcg)	- Breath-activated multi-dose DPI containing 60 individually sealed doses. A dose counter shows the number of doses remaining. It gives accurate and consistent drug delivery over a range of inspiratory flow rates (30-120L/minute). - Lactose powder is combined with the active medication for patients to taste and reassure them that they have inhaled a dose.
<u>Aerolizer</u>	Foradile (formoterol 12mcg)	- Breath-activated single-dose powder inhaler that comes with a sheet of 60 capsules in push-out foil sheet. One capsule is loaded into the inhaler and pierced before inhaling. - Gives consistent drug delivery over a range of inspiratory flow rates.
<u>Turbuhaler</u>	Bricanyl (terbutaline 500mcg); Pulmicort (budesonide 100mcg, 200mcg, 400mcg); Oxis (formoterol 6mcg, 12mcg);	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.

	Symbicort (formoterol 6mcg and budesonide 100mcg , formoterol 6mcg and budesonide 200mcg, formoterol 12mcg and budesonide 400mcg)	- Dose delivery is halved if the patient cannot produce inspiratory flow above 30L/min. Very few patients with COPD cannot produce a rate of >60L/min. - Produces very fine powder, so patients often don't taste anything. - Dose indicator shows when there are 20 doses remaining, and then when the inhaler is empty (it contains a drying agent that can be heard when the inhaler is shaken, which can be misinterpreted as available medication). - 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.
HandiHaler	Spiriva (tiotropium 18mcg)	
Breezhaler	Onbrez (indacaterol 150mcg, 300 mcg)	- Breath-activated single-dose powder inhaler - Capsules come in foil packs containing 30 capsules in a cardboard carton - Breezhaler inhalation device allows oral inhalation of the content of the capsule shell. One capsule is loaded into the inhaler and pierced before inhaling. - Gives consistent drug delivery over a range of inspiratory flow rates.
Genuair	Bretaris (aclidinium 322 microgram/dose)	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.
Ellipta	Breo (Fluticasone furoate 100 or 200 micrograms and vilanterol trifenate 25 micrograms/dose)	- 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. - 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. - Ipratropium can be combined with beta-agonist, but not with corticosteroid.
Nebulisers	Most nebulisers are electric. Some ultrasonic nebulisers are battery operated. These models are not heavy duty, but are ideal for travelling. There are also 12-volt pumps that plug into a car cigarette lighter. Use of inhaled corticosteroids requires a high-flow, heavy-duty pump.	

The products listed may not all be 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 FEV₁ 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 (PaO₂ > 60 mmHg, or 8 kPa; SpO₂ > 90%) and/or improvement in exercise capacity or nocturnal arterial oxygen saturation while using a practical oxygen delivery system.

What the patient needs to know

- Patients receiving oxygen therapy in the home, and their carers, should have the use clearly explained. That is, hours of use and flow rate, and any need to vary flow rates at given times. The equipment and its care, including how to obtain servicing or replacements, needs to be explained. The dangers of open flames (especially cigarettes, gas heaters and cookers) need to be emphasised.
- Flow should be set at the lowest rate needed to maintain a resting PaO₂ of 60 mmHg (8kPa) or SpO₂ > 88%. For patients with COPD, 0.5–2.0 L/min is usually sufficient. Flow rate should be increased by 1 L/min during exercise.
- Humidifiers are generally not needed at oxygen flow rates below 4 L/min.
- Extrasoft nasal prongs are recommended for continuous oxygen use, but may become uncomfortable at flow rates over 2–3 L/min and in the long term. Facemasks may be preferred for at least some of the time, although there are dangers of rebreathing exhaled CO₂ 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 PaO₂ and PaCO₂, 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 (SpO₂ < 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 PaCO₂ may depress ventilation, increase physiological dead space, and further increase arterial PaCO₂. This is suggested by the development of somnolence, headache and disorientation.
- In long-term oxygen therapy, the increase in arterial PaCO₂ 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.

List of Figures

Figure 1: COPD Phenotypes	15
Figure 2: Time-course of chronic obstructive pulmonary disease (COPD)(Fletcher and Peto, 1977) ...	16
Figure 3: Risk of occupational exposure for COPD from selected studies	17
Figure 4: Maximal expiratory flow-volume curves in severe chronic obstructive pulmonary disease (COPD) and chronic asthma	22

List of Boxes

Box 1: Levels of evidence	11
Box 2: Risk Factors for COPD(Global Initiative for Chronic Obstructive Lung Disease, 2009)	18
Box 3: Modified Medical Research Council (mMRC) Dyspnoea Scale for grading the severity of breathlessness during daily activities	20
Box 4: Classification of severity of chronic obstructive pulmonary disease (COPD)	24
Box 5: Assessment of acute response to inhaled beta-agonist at diagnosis	25
Box 6: Indication for referral to specialist respiratory outpatient services	26
Box 7: Comparison of outcomes for COPD management programs	80
Box 8: Patient support groups.....	86
Box 9: Indications for hospitalisation of patients with chronic obstructive pulmonary disease	93
Box 10: Indications for non-invasive or invasive ventilation	94
Box 11: Criteria for discharge	97
Box 12: Follow-up – initial and subsequent	98

References

- (GOLD), G. I. F. C. O. L. D. 2014. *Global Strategy for the Diagnosis, Management and Prevention of COPD* [Online]. Available: <http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html>.
- AARON, S. D., VANDEMHEEN, K. L., FERGUSON, D., MALTAIS, F., BOURBEAU, J., GOLDSTEIN, R., BALTER, M., O'DONNELL, D., MCIVOR, A., SHARMA, S., BISHOP, G., ANTHONY, J., COWIE, R., FIELD, S., HIRSCH, A., HERNANDEZ, P., RIVINGTON, R., ROAD, J., HOFFSTEIN, V., HODDER, R., MARCINIUK, D., MCCORMACK, D., FOX, G., COX, G., PRINS, H. B., FORD, G., BLESKIE, D., DOUCETTE, S., MAYERS, I., CHAPMAN, K., ZAMEL, N. & FITZGERALD, M. 2007. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*, 146, 545-55.
- ABERNETHY, A. P., CURROW, D. C., FRITH, P., FAZEKAS, B. S., MCHUGH, A. & BUI, C. 2003. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ*, 327, 523-8.
- ABERNETHY, A. P., MCDONALD, C. F., FRITH, P. A., CLARK, K., HERNDON, J. E., 2ND, MARCELLO, J., YOUNG, I. H., BULL, J., WILCOCK, A., BOOTH, S., WHEELER, J. L., TULSKY, J. A., CROCKETT, A. J. & CURROW, D. C. 2010. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet*, 376, 784-93.
- ABRAMSON, M. J., SCHATTLNER, R. L., SULAIMAN, N. D., BIRCH, K. E., SIMPSON, P. P., DEL COLLE, E. A., ARONI, R. A., WOLFE, R. & THIEN, F. C. 2010. Do spirometry and regular follow-up improve health outcomes in general practice patients with asthma or COPD? A cluster randomised controlled trial. *Med J Aust*, 193, 104-9.
- ABUSAID, G. H., BARBAGELATA, A., TUERO, E., MAHMOOD, A. & SHARMA, G. 2009. Diastolic dysfunction and COPD exacerbation. *Postgrad Med*, 121, 76-81.
- ACCESS ECONOMICS PTY LIMITED FOR THE AUSTRALIAN LUNG FOUNDATION 2008. Economic impact of COPD and cost-effective solutions.
- ADABAG, A. S., WASSIF, H. S., RICE, K., MITHANI, S., JOHNSON, D., BONAWITZ-CONLIN, J., WARD, H. B., MCFALLS, E. O., KUSKOWSKI, M. A. & KELLY, R. F. 2010. Preoperative pulmonary function and mortality after cardiac surgery. *Am Heart J*, 159, 691-7.
- ADAMS, S. G., SMITH, P. K., ALLAN, P. F., ANZUETO, A., PUGH, J. A. & CORNELL, J. E. 2007. Systematic review of the chronic care model in chronic obstructive pulmonary disease prevention and management. *Arch Intern Med*, 167, 551-61.
- AGARWAL, S. K., HEISS, G., BARR, R. G., CHANG, P. P., LOEHR, L. R., CHAMBLESS, L. E., SHAHAR, E., KITZMAN, D. W. & ROSAMOND, W. D. 2012. Airflow obstruction, lung function, and risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. *Eur J Heart Fail*, 14, 414-22.
- AGUSTI, A., DE TERESA, L., DE BACKER, W., ZVARICH, M. T., LOCANTORE, N., BARNES, N., BOURBEAU, J. & CRIM, C. 2014. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. *Eur Respir J*, 43, 763-72.
- AHMEDZAI, S., BALFOUR-LYNN, I. M., BEWICK, T., BUCHDAHL, R., COKER, R. K., CUMMIN, A. R., GRADWELL, D. P., HOWARD, L., INNES, J. A., JOHNSON, A. O., LIM, E., LIM, W. S., MCKINLAY, K. P., PARTRIDGE, M. R., POPPLESTONE, M., POZNIAK, A., ROBSON, A., SHOVLIN, C. L., SHRIKRISHNA, D., SIMONDS, A., TAIT, P. & THOMAS, M. 2011. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax*, 66 Suppl 1, i1-30.
- AIHW & CANCER AUSTRALIA 2011. Lung cancer in Australia: an overview. *Cancer series no. 64. Cat. no. CAN 58*. Canberra: AIHW.
- AKERO, A., EDVARSDEN, A., CHRISTENSEN, C. C., OWE, J. O., RYG, M. & SKJONSBORG, O. H. 2011. COPD and air travel: oxygen equipment and preflight titration of supplemental oxygen. *Chest*, 140, 84-90.

- AL-GHIMLAS, F. & TODD, D. C. 2010. Creatine supplementation for patients with COPD receiving pulmonary rehabilitation: a systematic review and meta-analysis. *Respirology*, 15, 785-95.
- ALBERT, R. K., CONNETT, J., BAILEY, W. C., CASABURI, R., COOPER, J. A., JR., CRINER, G. J., CURTIS, J. L., DRANSFIELD, M. T., HAN, M. K., LAZARUS, S. C., MAKE, B., MARCHETTI, N., MARTINEZ, F. J., MADINGER, N. E., MCEVOY, C., NIEWOEHNER, D. E., PORSASZ, J., PRICE, C. S., REILLY, J., SCANLON, P. D., SCIURBA, F. C., SCHARF, S. M., WASHKO, G. R., WOODRUFF, P. G. & ANTHONISEN, N. R. 2011. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*, 365, 689-98.
- ALIA, I., DE LA CAL, M. A., ESTEBAN, A., ABELLA, A., FERRER, R., MOLINA, F. J., TORRES, A., GORDO, F., ELIZALDE, J. J., DE PABLO, R., HUETE, A. & ANZUETO, A. 2011. Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. *Arch Intern Med*, 171, 1939-46.
- ALMAGRO, P., CABRERA, F. J., DIEZ, J., BOIXEDA, R., ALONSO ORTIZ, M. B., MURIO, C., SORIANO, J. B. & WORKING GROUP ON COPD, S. S. O. I. M. 2012. Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD: the EPOC en Servicios de medicina interna (ESMI) study. *Chest*, 142, 1126-33.
- ALMAGRO, P., SALVADO, M., GARCIA-VIDAL, C., RODRIGUEZ-CARBALLEIRA, M., DELGADO, M., BARREIRO, B., HEREDIA, J. L. & SORIANO, J. B. 2010. Recent improvement in long-term survival after a COPD hospitalisation. *Thorax*, 65, 298-302.
- ALTENBURG, W. A., DE GREEF, M. H., TEN HACKEN, N. H. & WEMPE, J. B. 2012. A better response in exercise capacity after pulmonary rehabilitation in more severe COPD patients. *Respir Med*, 106, 694-700.
- AMERICAN PSYCHIATRIC ASSOCIATION 2004. *Diagnostic and Statistical Manual of Mental Disorders (DSM IV)*, American Psychiatric Association.
- AMERICAN THORACIC SOCIETY 1995. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *Am J Respir Crit Care Med*, 152, S77-121.
- AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY 2003. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med*, 168, 818-900.
- ANDELL, P., KOUL, S., MARTINSSON, A., SUNDSTROM, J., JERNBERG, T., SMITH, J. G., JAMES, S., LINDAHL, B. & ERLINGE, D. 2014. Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. *Open Heart*, 1, e000002.
- ANSARI, Z., DUNT, D. & DHARMAGE, S. C. 2007. Variations in hospitalizations for chronic obstructive pulmonary disease in rural and urban Victoria, Australia. *Respirology*, 12, 874-80.
- ANTHONISEN, N. R., CONNETT, J. E. & MURRAY, R. P. 2002. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med*, 166, 675-9.
- ANTHONISEN, N. R., MANFREDI, J., WARREN, C. P., HERSHFELD, E. S., HARDING, G. K. & NELSON, N. A. 1987. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*, 106, 196-204.
- ANTIBIOTIC EXPERT GROUP. 2010. *Therapeutic guidelines: antibiotic. Version 14* [Online]. Melbourne: Therapeutic Guidelines Limited. Available: <http://www.tg.org.au/index.php?sectionid=41>.
- APPLETON, S., JONES, T., POOLE, P., PILOTTO, L., ADAMS, R., LASSERSON, T. J., SMITH, B. & MUHAMMAD, J. 2006a. Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 3, CD006101.
- APPLETON, S., POOLE, P., SMITH, B., VEALE, A., LASSERSON, T. J. & CHAN, M. M. 2006d. Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 3, CD001104.
- ARCHER, S. L., MIKE, D., CROW, J., LONG, W. & WEIR, E. K. 1996. A placebo-controlled trial of prostacyclin in acute respiratory failure in COPD. *Chest*, 109, 750-5.
- ARGYROPOULOU, P., PATAKAS, D., KOUKOU, A., VASILADIS, P. & GEORGOPOULOS, D. 1993. Buspirone effect on breathlessness and exercise performance in patients with chronic obstructive pulmonary disease. *Respiration*, 60, 216-20.

- ARYAL, S., DIAZ-GUZMAN, E. & MANNINO, D. M. 2014. Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes. *Int J Chron Obstruct Pulmon Dis*, 9, 1145-1154.
- ATLANTIS, E., FAHEY, P., COCHRANE, B., WITTERT, G. & SMITH, S. 2013. Endogenous testosterone level and testosterone supplementation therapy in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMJ Open*, 3.
- AUBIER, M. 1988. Pharmacotherapy of respiratory muscles. *Clin Chest Med*, 9, 311-24.
- AUBIN, H. J., BOBAK, A., BRITTON, J. R., ONCKEN, C., BILLING, C. B., JR., GONG, J., WILLIAMS, K. E. & REEVES, K. R. 2008. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax*, 63, 717-24.
- AUSTIN, M. A., WILLS, K. E., BLIZZARD, L., WALTERS, E. H. & WOOD-BAKER, R. 2010. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *BMJ*, 341, c5462.
- AUSTRALIAN BUREAU OF STATISTICS 2012. Australian Health Survey: First Results, 2011-12
- AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE 2008. Australia's Health: : The eleventh biennial health report of the Australian Institute of Health and Welfare. 11th ed. Canberra: Australian Institute of Health and Welfare.
- BADGETT, R. G., TANAKA, D. J., HUNT, D. K., JELLEY, M. J., FEINBERG, L. E., STEINER, J. F. & PETTY, T. L. 1993. Can moderate chronic obstructive pulmonary disease be diagnosed by historical and physical findings alone? *Am J Med*, 94, 188-96.
- BAILLIE, A. J., MATTICK, R. P., HALL, W. & WEBSTER, P. 1994. Meta-analytic review of the efficacy of smoking cessation interventions. *Drug Alcohol Rev*, 13, 157-70.
- BALDI, S., AQUILANI, R., PINNA, G. D., POGGI, P., DE MARTINI, A. & BRUSCHI, C. 2010. Fat-free mass change after nutritional rehabilitation in weight losing COPD: role of insulin, C-reactive protein and tissue hypoxia. *Int J Chron Obstruct Pulmon Dis*, 5, 29-39.
- BALDRICK, F. R., ELBORN, J. S., WOODSIDE, J. V., TREACY, K., BRADLEY, J. M., PATTERSON, C. C., SCHOCK, B. C., ENNIS, M., YOUNG, I. S. & MCKINLEY, M. C. 2012. Effect of fruit and vegetable intake on oxidative stress and inflammation in COPD: a randomised controlled trial. *Eur Respir J*, 39, 1377-84.
- BANSAL, V., HILL, K., DOLMAGE, T. E., BROOKS, D., WOON, L. J. & GOLDSTEIN, R. S. 2008. Modifying track layout from straight to circular has a modest effect on the 6-min walk distance. *Chest*, 133, 1155-60.
- BARANIAK, A. & SHEFFIELD, D. 2011. The efficacy of psychologically based interventions to improve anxiety, depression and quality of life in COPD: a systematic review and meta-analysis. *Patient Educ Couns*, 83, 29-36.
- BARBERA, J. A., ROGER, N., ROCA, J., ROVIRA, I., HIGENBOTTAM, T. W. & RODRIGUEZ-ROISIN, R. 1996. Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. *Lancet*, 347, 436-40.
- BARNES, P. J. 2003. Theophylline: new perspectives for an old drug. *Am J Respir Crit Care Med*, 167, 813-8.
- BARNES, P. J. & CELLI, B. R. 2009. Systemic manifestations and comorbidities of COPD. *Eur Respir J*, 33, 1165-85.
- BARR, R. G., BLUEMKE, D. A., AHMED, F. S., CARR, J. J., ENRIGHT, P. L., HOFFMAN, E. A., JIANG, R., KAWUT, S. M., KRONMAL, R. A., LIMA, J. A., SHAHAR, E., SMITH, L. J. & WATSON, K. E. 2010. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med*, 362, 217-27.
- BARR, R. G., BOURBEAU, J., CAMARGO, C. A. & RAM, F. S. 2005. Tiotropium for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD002876.
- BARR, R. G., BOURBEAU, J., CAMARGO, C. A. & RAM, F. S. 2006. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. *Thorax*, 61, 854-62.
- BARTLETT, Y. K., SHEERAN, P. & HAWLEY, M. S. 2014. Effective behaviour change techniques in smoking cessation interventions for people with chronic obstructive pulmonary disease: a meta-analysis. *Br J Health Psychol*, 19, 181-203.
- BATEMAN, E. D., FERGUSON, G. T., BARNES, N., GALLAGHER, N., GREEN, Y., HENLEY, M. & BANERJI, D. 2013. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur Respir J*, 42, 1484-94.

- BELMAN, M. J., BOTNICK, W. C. & SHIN, J. W. 1996. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 153, 967-75.
- BENDITT, J. O. & ALBERT, R. K. 1997. Surgical options for patients with advanced emphysema. *Clin Chest Med*, 18, 577-93.
- BENEY, J., BERO, L. A. & BOND, C. 2000. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes. *Cochrane Database Syst Rev*, CD000336.
- BENZO, R., FARRELL, M. H., CHANG, C. C., MARTINEZ, F. J., KAPLAN, R., REILLY, J., CRINER, G., WISE, R., MAKE, B., LUKETICH, J., FISHMAN, A. P. & SCIURBA, F. C. 2009. Integrating health status and survival data: the palliative effect of lung volume reduction surgery. *Am J Respir Crit Care Med*, 180, 239-46.
- BERGER, R. & SMITH, D. 1988. Effect of inhaled metaproterenol on exercise performance in patients with stable "fixed" airway obstruction. *Am Rev Respir Dis*, 138, 624-9.
- BHATT, S. P., KIM, Y. I., WELLS, J. M., BAILEY, W. C., RAMSDELL, J. W., FOREMAN, M. G., JENSEN, R. L., STINSON, D. S., WILSON, C. G., LYNCH, D. A., MAKE, B. J. & DRANSFIELD, M. T. 2014a. FEV(1)/FEV(6) to diagnose airflow obstruction. Comparisons with computed tomography and morbidity indices. *Ann Am Thorac Soc*, 11, 335-41.
- BHATT, S. P., NANDA, S. & KINTZER, J. S. 2012. Arrhythmias as trigger for acute exacerbations of chronic obstructive pulmonary disease. *Respir Med*, 106, 1134-8.
- BHATT, S. P., SIEREN, J. C., DRANSFIELD, M. T., WASHKO, G. R., NEWELL, J. D., JR., STINSON, D. S., ZAMBA, G. K. & HOFFMAN, E. A. 2014b. Comparison of spirometric thresholds in diagnosing smoking-related airflow obstruction. *Thorax*, 69, 409-14.
- BIERUT, L. J. 2010. Convergence of genetic findings for nicotine dependence and smoking related diseases with chromosome 15q24-25. *Trends Pharmacol Sci*, 31, 46-51.
- BISCHOFF, E. W., AKKERMANS, R., BOURBEAU, J., VAN WEEL, C., VERCOULEN, J. H. & SCHERMER, T. R. 2012. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. *BMJ*, 345, e7642.
- BLACK, P., STAYKOVA, T., CHACKO, E., RAM, F. S. & POOLE, P. 2003. Prophylactic antibiotic therapy for chronic bronchitis. *Cochrane Database Syst Rev*, CD004105.
- BLACKSTOCK, F. & WEBSTER, K. 2007. Disease-specific health education for COPD: a systematic review of changes in health outcomes. *Health Educ Res*, 22, 703-17.
- BLACKSTOCK, F. C., WEBSTER, K. E., MCDONALD, C. F. & HILL, C. J. 2014. Comparable improvements achieved in chronic obstructive pulmonary disease through pulmonary rehabilitation with and without a structured educational intervention: a randomized controlled trial. *Respirology*, 19, 193-202.
- BLANC, P. D., IRIBARREN, C., TRUPIN, L., EARNEST, G., KATZ, P. P., BALMES, J., SIDNEY, S. & EISNER, M. D. 2009. Occupational exposures and the risk of COPD: dusty trades revisited. *Thorax*, 64, 6-12.
- BLANCO, I., DE SERRES, F. J., FERNANDEZ-BUSTILLO, E., LARA, B. & MIRAVITLLES, M. 2006. Estimated numbers and prevalence of PI*S and PI*Z alleles of alpha1-antitrypsin deficiency in European countries. *Eur Respir J*, 27, 77-84.
- BOLTON, C. E., WATERS, C. S., PEIRCE, S. & ELWYN, G. 2011. Insufficient evidence of benefit: a systematic review of home telemonitoring for COPD. *J Eval Clin Pract*, 17, 1216-22.
- BORGHI-SILVA, A., BALDISSERA, V., SAMPAIO, L. M., PIRES-DILORENZO, V. A., JAMAMI, M., DEMONTE, A., MARCHINI, J. S. & COSTA, D. 2006. L-carnitine as an ergogenic aid for patients with chronic obstructive pulmonary disease submitted to whole-body and respiratory muscle training programs. *Braz J Med Biol Res*, 39, 465-74.
- BORRILL, Z., HOUGHTON, C., SULLIVAN, P. J. & SESTINI, P. 2003. Retrospective analysis of evidence base for tests used in diagnosis and monitoring of disease in respiratory medicine. *BMJ*, 327, 1136-8.
- BOTT, J., CARROLL, M. P., CONWAY, J. H., KEILTY, S. E., WARD, E. M., BROWN, A. M., PAUL, E. A., ELLIOTT, M. W., GODFREY, R. C., WEDZICHA, J. A. & ET AL. 1993. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet*, 341, 1555-7.

- BOUDESTEIN, L. C., RUTTEN, F. H., CRAMER, M. J., LAMMERS, J. W. & HOES, A. W. 2009. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. *Eur J Heart Fail*, 11, 1182-8.
- BOURBEAU, J., JULIEN, M., MALTAIS, F., ROULEAU, M., BEAUPRE, A., BEGIN, R., RENZI, P., NAULT, D., BORYCKI, E., SCHWARTZMAN, K., SINGH, R. & COLLET, J. P. 2003. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med*, 163, 585-91.
- BOUTOU, A. K., KARRAR, S., HOPKINSON, N. S. & POLKEY, M. I. 2013. Anemia and survival in chronic obstructive pulmonary disease: a dichotomous rather than a continuous predictor. *Respiration*, 85, 126-31.
- BOUTOU, A. K., PITSIU, G. G., STANOPOULOS, I., KONTAKIOTIS, T., KYRIAZIS, G. & ARGYROPOULOU, P. 2012. Levels of inflammatory mediators in chronic obstructive pulmonary disease patients with anemia of chronic disease: a case-control study. *QJM*, 105, 657-63.
- BOUTOU, A. K., STANOPOULOS, I., PITSIU, G. G., KONTAKIOTIS, T., KYRIAZIS, G., SICHLETIDIS, L. & ARGYROPOULOU, P. 2011. Anemia of chronic disease in chronic obstructive pulmonary disease: a case-control study of cardiopulmonary exercise responses. *Respiration*, 82, 237-45.
- BRADLEY, J. M., LASSERSON, T., ELBORN, S., MACMAHON, J. & O'NEILL, B. 2007. A systematic review of randomized controlled trials examining the short-term benefit of ambulatory oxygen in COPD. *Chest*, 131, 278-85.
- BRADLEY, J. M. & O'NEILL, B. 2005. Short term ambulatory oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD004356.
- BRAIDO, F., BAIARDINI, I., CAZZOLA, M., BRUSSELLE, G., MARUGO, F. & CANONICA, G. W. 2013. Long-acting bronchodilators improve health related quality of life in patients with COPD. *Respir Med*, 107, 1465-80.
- BRITISH THORACIC SOCIETY 1997. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax*, 52, S1-S28.
- BRITISH THORACIC SOCIETY 2008a. British Guideline on the Management of Asthma. *Thorax*, 63 Suppl 4, iv1-121.
- BRITISH THORACIC SOCIETY 2008b. BTS statement on criteria for specialist referral, admission, discharge and follow-up for adults with respiratory disease. *Thorax*, 63 Suppl 1, i1-i16.
- BRITTON, J. & KNOX, A. 1999. Helping people to stop smoking: the new smoking cessation guidelines. *Thorax*, 54, 1-2.
- BROCHARD, L., MANCEBO, J., WYSOCKI, M., LOFASO, F., CONTI, G., RAUSS, A., SIMONNEAU, G., BENITO, S., GASPARETTO, A., LEMAIRE, F. & ET AL. 1995. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*, 333, 817-22.
- BROEKHUIZEN, R., WOUTERS, E. F., CREUTZBERG, E. C., WELING-SCHEEPERS, C. A. & SCHOLS, A. M. 2005. Polyunsaturated fatty acids improve exercise capacity in chronic obstructive pulmonary disease. *Thorax*, 60, 376-82.
- BROOKS, D., KRIP, B., MANGOVSKI-ALZAMORA, S. & GOLDSTEIN, R. S. 2002. The effect of postrehabilitation programmes among individuals with chronic obstructive pulmonary disease. *Eur Respir J*, 20, 20-9.
- BRUSKE, I., THIERING, E., HEINRICH, J., HUSTER, K. M. & NOWAK, D. 2014. Respirable quartz dust exposure and airway obstruction: a systematic review and meta-analysis. *Occup Environ Med*, 71, 583-9.
- BRYANT, J., MCDONALD, V. M., BOYES, A., SANSON-FISHER, R., PAUL, C. & MELVILLE, J. 2013. Improving medication adherence in chronic obstructive pulmonary disease: a systematic review. *Respir Res*, 14, 109.
- BUCKNALL, C. E., MILLER, G., LLOYD, S. M., CLELAND, J., MCCLUSKEY, S., COTTON, M., STEVENSON, R. D., COTTON, P. & MCCONNACHIE, A. 2012. Glasgow supported self-management trial (GSuST) for patients with moderate to severe COPD: randomised controlled trial. *BMJ*, 344, e1060.
- BULA, C. J., WIETLISBACH, V., BURNAND, B. & YERSIN, B. 2001. Depressive symptoms as a predictor of 6-month outcomes and services utilization in elderly medical inpatients. *Arch Intern Med*, 161, 2609-15.

- BULLEN, C., HOWE, C., LAUGESSEN, M., MCROBBIE, H., PARAG, V., WILLIMAN, J. & WALKER, N. 2013. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*, 382, 1629-37.
- BURGEL, P. R., NESME-MEYER, P., CHANEZ, P., CAILLAUD, D., CARRE, P., PEREZ, T. & ROCHE, N. 2009. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. *Chest*, 135, 975-82.
- BURNS, K. E., ADHIKARI, N. K., KEENAN, S. P. & MEADE, M. O. 2010. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev*, CD004127.
- BURROWS, B., KNUDSON, R., CLINE, M. & LEBOWITZ, M. 1977. Quantitative relationships between cigarette smoking and ventilatory function. *American Rev Respir Dis*, 115, 195-205.
- BURSI, F., VASSALLO, R., WESTON, S. A., KILLIAN, J. M. & ROGER, V. L. 2010. Chronic obstructive pulmonary disease after myocardial infarction in the community. *Am Heart J*, 160, 95-101.
- CAHILL, K., LANCASTER, T. & GREEN, N. 2010. Stage-based interventions for smoking cessation. *Cochrane Database Syst Rev*, CD004492.
- CAHILL, K., STEAD, L. F. & LANCASTER, T. 2008. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*, CD006103.
- CAHILL, K., STEVENS, S., PERERA, R. & LANCASTER, T. 2013. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*, 5, CD009329.
- CAHILL, K. & USSHER, M. 2007. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. *Cochrane Database Syst Rev*, CD005353.
- CALVERLEY, P. M., ANDERSON, J. A., CELLI, B., FERGUSON, G. T., JENKINS, C., JONES, P. W., CRIM, C., WILLITS, L. R., YATES, J. C. & VESTBO, J. 2010. Cardiovascular events in patients with COPD: TORCH study results. *Thorax*, 65, 719-25.
- CALVERLEY, P. M., ANDERSON, J. A., CELLI, B., FERGUSON, G. T., JENKINS, C., JONES, P. W., YATES, J. C. & VESTBO, J. 2007. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*, 356, 775-89.
- CALVERLEY, P. M., RABE, K. F., GOEHRING, U. M., KRISTIANSEN, S., FABBRI, L. M. & MARTINEZ, F. J. 2009. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*, 374, 685-94.
- CALVERLEY, P. M., STOCKLEY, R. A., SEEMUNGAL, T. A., HAGAN, G., WILLITS, L. R., RILEY, J. H. & WEDZICHA, J. A. 2011. Reported pneumonia in patients with COPD: findings from the INSPIRE study. *Chest*, 139, 505-12.
- CAMP, P. G., COXSON, H. O., LEVY, R. D., PILLAI, S. G., ANDERSON, W., VESTBO, J., KENNEDY, S. M., SILVERMAN, E. K., LOMAS, D. A. & PARE, P. D. 2009. Sex differences in emphysema and airway disease in smokers. *Chest*, 136, 1480-8.
- CANCER COUNCIL AUSTRALIA 2004. Clinical Practice Guidelines for the Prevention, Diagnosis and Management of Lung Cancer. Sydney.
- CAPONNETTO, P., CAMPAGNA, D., CIBELLA, F., MORJARIA, J. B., CARUSO, M., RUSSO, C. & POLOSA, R. 2013. Efficiency and Safety of an eElectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One*, 8, e66317.
- CARR, A. B. & EBBERT, J. 2012. Interventions for tobacco cessation in the dental setting. *Cochrane Database Syst Rev*, 6, CD005084.
- CASANOVA, C., CELLI, B. R., TOST, L., SORIANO, E., ABREU, J., VELASCO, V. & SANTOLARIA, F. 2000. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. *Chest*, 118, 1582-90.
- CASANOVA, C., COTE, C., DE TORRES, J. P., AGUIRRE-JAIME, A., MARIN, J. M., PINTO-PLATA, V. & CELLI, B. R. 2005. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 171, 591-7.
- CASAS, A., TROOSTERS, T., GARCIA-AYMERICH, J., ROCA, J., HERNANDEZ, C., ALONSO, A., DEL POZO, F., DE TOLEDO, P., ANTO, J. M., RODRIGUEZ-ROISIN, R. & DECRAMER, M. 2006. Integrated care prevents hospitalisations for exacerbations in COPD patients. *Eur Respir J*, 28, 123-30.

- CATES, C. J., CRILLY, J. A. & ROWE, B. H. 2006. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev*, CD000052.
- CAZZOLA, M., CALZETTA, L., BETTONCELLI, G., CRICELLI, C., ROMEO, F., MATERA, M. G. & ROGLIANI, P. 2012. Cardiovascular disease in asthma and COPD: a population-based retrospective cross-sectional study. *Respir Med*, 106, 249-56.
- CECERE, L. M., LITTMAN, A. J., SLATORE, C. G., UDRIS, E. M., BRYSON, C. L., BOYKO, E. J., PIERSON, D. J. & AU, D. H. 2011. Obesity and COPD: associated symptoms, health-related quality of life, and medication use. *COPD*, 8, 275-84.
- CELLI, B., DECRAMER, M., KESTEN, S., LIU, D., MEHRA, S. & TASHKIN, D. P. 2009. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 180, 948-55.
- CELLI, B. R. 1995. Pulmonary rehabilitation in patients with COPD. *Am J Respir Crit Care Med*, 152, 861-4.
- CELLI, B. R., COTE, C. G., LAREAU, S. C. & MEEK, P. M. 2008. Predictors of Survival in COPD: more than just the FEV1. *Respir Med*, 102 Suppl 1, S27-35.
- CELLI, B. R., COTE, C. G., MARIN, J. M., CASANOVA, C., MONTES DE OCA, M., MENDEZ, R. A., PINTO PLATA, V. & CABRAL, H. J. 2004. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*, 350, 1005-12.
- CHAMBELLAN, A., CHAILLEUX, E., SIMILOWSKI, T. & GROUP, A. O. 2005. Prognostic value of the hematocrit in patients with severe COPD receiving long-term oxygen therapy. *Chest*, 128, 1201-8.
- CHANDRA, D., WISE, R. A., KULKARNI, H. S., BENZO, R. P., CRINER, G., MAKE, B., SLIVKA, W. A., RIES, A. L., REILLY, J. J., MARTINEZ, F. J. & SCIURBA, F. C. 2012. Optimizing the 6-min walk test as a measure of exercise capacity in COPD. *Chest*, 142, 1545-52.
- CHANG, C. L., ROBINSON, S. C., MILLS, G. D., SULLIVAN, G. D., KARALUS, N. C., MCLACHLAN, J. D. & HANCOX, R. J. 2011. Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. *Thorax*, 66, 764-8.
- CHAOUAT, A., BUGNET, A. S., KADAOU, N., SCHOTT, R., ENACHE, I., DUCOLONE, A., EHRHART, M., KESSLER, R. & WEITZENBLUM, E. 2005. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 172, 189-94.
- CHAOUAT, A., NAEIJE, R. & WEITZENBLUM, E. 2008. Pulmonary hypertension in COPD. *Eur Respir J*, 32, 1371-85.
- CHAOUAT, A., WEITZENBLUM, E., KRIEGER, J., IFOUNDZA, T., OSWALD, M. & KESSLER, R. 1995. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. *Am J Respir Crit Care Med*, 151, 82-6.
- CHAPMAN, K. R., BEEH, K. M., BEIER, J., BATEMAN, E. D., D'URZO, A., NUTBROWN, R., HENLEY, M., CHEN, H., OVEREND, T. & D'ANDREA, P. 2014. A blinded evaluation of the efficacy and safety of glycopyrronium, a once-daily long-acting muscarinic antagonist, versus tiotropium, in patients with COPD: the GLOW5 study. *BMC Pulm Med*, 14, 4.
- CHAPMAN, K. R., RENNARD, S. I., DOGRA, A., OWEN, R., LASSEN, C. & KRAMER, B. 2011. Long-term safety and efficacy of indacaterol, a long-acting beta-agonist, in subjects with COPD: a randomized, placebo-controlled study. *Chest*, 140, 68-75.
- CHAVANNES, N., VOLLENBERG, J. J., VAN SCHAYCK, C. P. & WOUTERS, E. F. 2002. Effects of physical activity in mild to moderate COPD: a systematic review. *Br J Gen Pract*, 52, 574-8.
- CHEN, D., RESTREPO, M. I., FINE, M. J., PUGH, M. J., ANZUETO, A., METERSKY, M. L., NAKASHIMA, B., GOOD, C. & MORTENSEN, E. M. 2011. Observational study of inhaled corticosteroids on outcomes for COPD patients with pneumonia. *Am J Respir Crit Care Med*, 184, 312-6.
- CHEYNE, L., IRVIN-SELLERS, M. J. & WHITE, J. 2013. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 9, CD009552.
- CHONG, J., KARNER, C. & POOLE, P. 2012. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 9, CD009157.
- CHONG, J., LEUNG, B. & POOLE, P. 2013. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 11, CD002309.

- CHRYSTYN, H., MULLEY, B. A. & PEAKE, M. D. 1988. Dose response relation to oral theophylline in severe chronic obstructive airways disease. *BMJ*, 297, 1506-10.
- CINDY NG, L. W., MACKNEY, J., JENKINS, S. & HILL, K. 2012. Does exercise training change physical activity in people with COPD? A systematic review and meta-analysis. *Chron Respir Dis*, 9, 17-26.
- CIVLJAK, M., STEAD, L. F., HARTMANN-BOYCE, J., SHEIKH, A. & CAR, J. 2013. Internet-based interventions for smoking cessation. *Cochrane Database Syst Rev*, 7, CD007078.
- CLAESSENS, M. T., LYNN, J., ZHONG, Z., DESBIENS, N. A., PHILLIPS, R. S., WU, A. W., HARRELL, F. E., JR. & CONNORS, A. F., JR. 2000. Dying with lung cancer or chronic obstructive pulmonary disease: insights from SUPPORT. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *J Am Geriatr Soc*, 48, S146-53.
- CLINI, E., STURANI, C., ROSSI, A., VIAGGI, S., CORRADO, A., DONNER, C. F. & AMBROSINO, N. 2002. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J*, 20, 529-38.
- COCKCROFT, A., BEAUMONT, A., ADAMS, L. & GUZ, A. 1985. Arterial oxygen desaturation during treadmill and bicycle exercise in patients with chronic obstructive airways disease. *Clin Sci (Lond)*, 68, 327-32.
- COE, J. W., BROOKS, P. R., VETELINO, M. G., WIRTZ, M. C., ARNOLD, E. P., HUANG, J., SANDS, S. B., DAVIS, T. I., LEBEL, L. A., FOX, C. B., SHRIKHANDE, A., HEYM, J. H., SCHAEFFER, E., ROLLEMA, H., LU, Y., MANSBACH, R. S., CHAMBERS, L. K., ROVETTI, C. C., SCHULZ, D. W., TINGLEY, F. D., 3RD & O'NEILL, B. T. 2005. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *J Med Chem*, 48, 3474-7.
- COLLINS, P. F., STRATTON, R. J. & ELIA, M. 2012. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Am J Clin Nutr*, 95, 1385-95.
- CONNORS, A. F., JR., DAWSON, N. V., THOMAS, C., HARRELL, F. E., JR., DESBIENS, N., FULKERSON, W. J., KUSSIN, P., BELLAMY, P., GOLDMAN, L. & KNAUS, W. A. 1996. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) [published erratum appears in Am J Respir Crit Care Med 1997;155:386]. *Am J Respir Crit Care Med*, 154, 959-67.
- COOPER, J. D., TRULOCK, E. P., TRIANTAFILLOU, A. N., PATTERSON, G. A., POHL, M. S., DELONEY, P. A., SUNDARESAN, R. S. & ROPER, C. L. 1995. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg*, 109, 106-16; discussion 116-9.
- COPE, S., DONOHUE, J. F., JANSEN, J. P., KRAEMER, M., CAPKUN-NIGGLI, G., BALDWIN, M., BUCKLEY, F., ELLIS, A. & JONES, P. 2013. Comparative efficacy of long-acting bronchodilators for COPD: a network meta-analysis. *Respir Res*, 14, 100.
- COSIO, B. G., IGLESIAS, A., RIOS, A., NOGUERA, A., SALA, E., ITO, K., BARNES, P. J. & AGUSTI, A. 2009. Low-dose theophylline enhances the anti-inflammatory effects of steroids during exacerbations of COPD. *Thorax*, 64, 424-9.
- COTE, C., ZILBERBERG, M. D., MODY, S. H., DORDELLY, L. J. & CELLI, B. 2007. Haemoglobin level and its clinical impact in a cohort of patients with COPD. *Eur Respir J*, 29, 923-9.
- COVENTRY, P. A., BOWER, P., KEYWORTH, C., KENNING, C., KNOPP, J., GARRETT, C., HIND, D., MALPASS, A. & DICKENS, C. 2013. The effect of complex interventions on depression and anxiety in chronic obstructive pulmonary disease: systematic review and meta-analysis. *PLoS One*, 8, e60532.
- COVENTRY, P. A. & HIND, D. 2007. Comprehensive pulmonary rehabilitation for anxiety and depression in adults with chronic obstructive pulmonary disease: Systematic review and meta-analysis. *J Psychosom Res*, 63, 551-65.
- CRANSTON, J. M., CROCKETT, A. J., MOSS, J. R. & ALPERS, J. H. 2005. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD001744.
- CREWS, W. D., JEFFERSON, A. L., BOLDUC, T., ELLIOTT, J. B., FERRO, N. M., BROSHEK, D. K., BARTH, J. T. & ROBBINS, M. K. 2001. Neuropsychological dysfunction in patients suffering from end-stage chronic obstructive pulmonary disease. *Arch Clin Neuropsychol*, 16, 643-52.
- CRINER, G. J., CONNETT, J. E., AARON, S. D., ALBERT, R. K., BAILEY, W. C., CASABURI, R., COOPER, J. A., JR., CURTIS, J. L., DRANSFIELD, M. T., HAN, M. K., MAKE, B., MARCHETTI,

- N., MARTINEZ, F. J., NIEWOEHNER, D. E., SCANLON, P. D., SCIURBA, F. C., SCHARF, S. M., SIN, D. D., VOELKER, H., WASHKO, G. R., WOODRUFF, P. G. & LAZARUS, S. C. 2014. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med*, 370, 2201-10.
- CRINER, G. J., CORDOVA, F., STERNBERG, A. L. & MARTINEZ, F. J. 2011. The National Emphysema Treatment Trial (NETT) Part II: Lessons learned about lung volume reduction surgery. *Am J Respir Crit Care Med*, 184, 881-93.
- CUI, H., WEI, Z. M., FAN, L., ZHANG, M., LIU, L. & HU, Y. X. 2012. [Clinical predictive value of hemoglobin level in mortality of hospitalized COPD patients]. *Zhongguo Ying Yong Sheng Li Xue Za Zhi*, 28, 394-7.
- CUI, L., GALLAGHER, L. G., RAY, R. M., LI, W., GAO, D., ZHANG, Y., VEDAL, S., THOMAS, D. B. & CHECKOWAY, H. 2011. Unexpected excessive chronic obstructive pulmonary disease mortality among female silk textile workers in Shanghai, China. *Occup Environ Med*, 68, 883-7.
- D'URZO, A., FERGUSON, G. T., VAN NOORD, J. A., HIRATA, K., MARTIN, C., HORTON, R., LU, Y., BANERJI, D. & OVEREND, T. 2011. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. *Respir Res*, 12, 156.
- DAGA, M. K., CHHABRA, R., SHARMA, B. & MISHRA, T. K. 2003. Effects of exogenous vitamin E supplementation on the levels of oxidants and antioxidants in chronic obstructive pulmonary disease. *J Biosci*, 28, 7-11.
- DAHL, R., CHAPMAN, K. R., RUDOLF, M., MEHTA, R., KHO, P., ALAGAPPAN, V. K., CHEN, H. & BANERJI, D. 2013. Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: the ENLIGHTEN study. *Respir Med*, 107, 1558-67.
- DAHL, R., CHUNG, K. F., BUHL, R., MAGNUSSEN, H., NONIKOV, V., JACK, D., BLEASDALE, P., OWEN, R., HIGGINS, M. & KRAMER, B. 2010. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax*, 65, 473-9.
- DAL NEGRO, R. W., AQUILANI, R., BERTACCO, S., BOSCHI, F., MICHELETTO, C. & TOGNELLA, S. 2010. Comprehensive effects of supplemented essential amino acids in patients with severe COPD and sarcopenia. *Monaldi Arch Chest Dis*, 73, 25-33.
- DANIELS, J. M., SNIJDERS, D., DE GRAAFF, C. S., VLASPOOLDER, F., JANSEN, H. M. & BOERSMA, W. G. 2010. Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 181, 150-7.
- DAVIS, A. L., ARANDA, C. P., SCHIFFMAN, G. & CHRISTIANSON, L. C. 1987. Pneumococcal infection and immunologic response to pneumococcal vaccine in chronic obstructive pulmonary disease. A pilot study. *Chest*, 92, 204-12.
- DE GODOY, D. V. & DE GODOY, R. F. 2003. A randomized controlled trial of the effect of psychotherapy on anxiety and depression in chronic obstructive pulmonary disease. *Arch Phys Med Rehabil*, 84, 1154-7.
- DE MIGUEL-DIEZ, J., CARRASCO-GARRIDO, P., REJAS-GUTIERREZ, J., MARTIN-CENTENO, A., GOBARTT-VAZQUEZ, E., HERNANDEZ-BARRERA, V., DE MIGUEL, A. G. & JIMENEZ-GARCIA, R. 2010. The influence of heart disease on characteristics, quality of life, use of health resources, and costs of COPD in primary care settings. *BMC Cardiovasc Disord*, 10, 8.
- DE SERRES, F. J. 2002. Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency: summary of an analysis of published genetic epidemiologic surveys. *Chest*, 122, 1818-29.
- DE TORRES, J. P., MARIN, J. M., CASANOVA, C., COTE, C., CARRIZO, S., CORDOBA-LANUS, E., BAZ-DAVILA, R., ZULUETA, J. J., AGUIRRE-JAIME, A., SAETTA, M., COSIO, M. G. & CELLI, B. R. 2011. Lung cancer in patients with chronic obstructive pulmonary disease-- incidence and predicting factors. *Am J Respir Crit Care Med*, 184, 913-9.
- DEAN, M. M. 2008. End-of-life care for COPD patients. *Prim Care Respir J*, 17, 46-50.
- DECRAMER, M., ANZUETO, A., KERWIN, E., KAELEN, T., RICHARD, N., CRATER, G., TABBERER, M., HARRIS, S. & CHURCH, A. 2014. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med*, 2, 472-86.

- DECRAMER, M., CELLI, B., KESTEN, S., LYSTIG, T., MEHRA, S. & TASHKIN, D. P. 2009. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet*, 374, 1171-8.
- DECRAMER, M., DE BENEDETTO, F., DEL PONTE, A. & MARINARI, S. 2005. Systemic effects of COPD. *Respir Med*, 99 Suppl B, S3-10.
- DECRAMER, M., DE BOCK, V. & DOM, R. 1996. Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 153, 1958-64.
- DECRAMER, M., LACQUET, L. M., FAGARD, R. & ROGIERS, P. 1994. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med*, 150, 11-6.
- DECRAMER, M. & STAS, K. J. 1992. Corticosteroid-induced myopathy involving respiratory muscles in patients with chronic obstructive pulmonary disease or asthma. *Am Rev Respir Dis*, 146, 800-2.
- DESLEE, G., KLOOSTER, K., HETZEL, M., STANZEL, F., KESSLER, R., MARQUETTE, C. H., WITT, C., BLAAS, S., GESIERICH, W., HERTH, F. J., HETZEL, J., VAN RIKXOORT, E. M. & SLEBOS, D. J. 2014. Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. *Thorax*, 69, 980-6.
- DI MARCO, F., VERGA, M., REGGENTE, M., MARIA CASANOVA, F., SANTUS, P., BLASI, F., ALLEGRA, L. & CENTANNI, S. 2006. Anxiety and depression in COPD patients: The roles of gender and disease severity. *Respir Med*, 100, 1767-74.
- DIAZ-GUZMAN, E., ARYAL, S. & MANNINO, D. M. 2012. Occupational chronic obstructive pulmonary disease: an update. *Clin Chest Med*, 33, 625-36.
- DIJK, W. D., BEMT, L., HAAK-RONGEN, S., BISCHOFF, E., WEEL, C., VEEN, J. C. & SCHERMER, T. R. 2011. Multidimensional prognostic indices for use in COPD patient care. A systematic review. *Respir Res*, 12, 151.
- DOBLER, C. C., WONG, K. K. & MARKS, G. B. 2009. Associations between statins and COPD: a systematic review. *BMC Pulm Med*, 9, 32.
- DODD, J. W., CHARLTON, R. A., VAN DEN BROEK, M. D. & JONES, P. W. 2013. Cognitive dysfunction in patients hospitalized with acute exacerbation of COPD. *Chest*, 144, 119-27.
- DOLMAGE, T. E., HILL, K., EVANS, R. A. & GOLDSTEIN, R. S. 2011. Has my patient responded? Interpreting clinical measurements such as the 6-minute-walk test. *Am J Respir Crit Care Med*, 184, 642-6.
- DONALDSON, G. C., HURST, J. R., SMITH, C. J., HUBBARD, R. B. & WEDZICHA, J. A. 2010. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest*, 137, 1091-7.
- DONG, Y. H., LIN, H. H., SHAU, W. Y., WU, Y. C., CHANG, C. H. & LAI, M. S. 2013. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. *Thorax*, 68, 48-56.
- DONOHUE, J. F., FOGARTY, C., LOTVALL, J., MAHLER, D. A., WORTH, H., YORGANCIOGLU, A., IQBAL, A., SWALES, J., OWEN, R., HIGGINS, M. & KRAMER, B. 2010. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. *Am J Respir Crit Care Med*, 182, 155-62.
- DONOHUE, J. F., MALEKI-YAZDI, M. R., KILBRIDE, S., MEHTA, R., KALBERG, C. & CHURCH, A. 2013. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med*, 107, 1538-46.
- DONOHUE, J. F., NIEWOEHNER, D., BROOKS, J., O'DELL, D. & CHURCH, A. 2014. Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease: results from a 52-week, randomized, double-blind, placebo-controlled study. *Respir Res*, 15, 78.
- DOWSON, C. A., TOWN, G. I., FRAMPTON, C. & MULDER, R. T. 2004. Psychopathology and illness beliefs influence COPD self-management. *J Psychosom Res*, 56, 333-40.
- DRANSFIELD, M. T., BOURBEAU, J., JONES, P. W., HANANIA, N. A., MAHLER, D. A., VESTBO, J., WACHTEL, A., MARTINEZ, F. J., BARNHART, F., SANFORD, L., LETTIS, S., CRIM, C. & CALVERLEY, P. M. 2013. Once-daily inhaled fluticasone furoate and vilanterol versus

- vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med*, 1, 210-23.
- DRANSFIELD, M. T., FELDMAN, G., KORENBLAT, P., LAFORCE, C. F., LOCANTORE, N., PISTOLESI, M., WATKINS, M. L., CRIM, C. & MARTINEZ, F. J. 2014. Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients. *Respir Med*, 108, 1171-9.
- DRANSFIELD, M. T., ROWE, S. M., JOHNSON, J. E., BAILEY, W. C. & GERALD, L. B. 2007. Beta-blocker use and the risk of death in hospitalized patients with acute exacerbations of COPD. *Thorax*, thx.2007.081893.
- DRUMMOND, M. B., HANSEL, N. N., CONNETT, J. E., SCANLON, P. D., TASHKIN, D. P. & WISE, R. A. 2012. Spirometric predictors of lung function decline and mortality in early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 185, 1301-6.
- DYER, F., MARRINER, P., CHEEMA, K. & BOTT, J. 2011. Is a practice incremental shuttle walk test really necessary? *Chron Respir Dis*, 8, 201-5.
- EFFING, T., MONNINKHOF, E. M., VAN DER VALK, P. D., VAN DER PALEN, J., VAN HERWAARDEN, C. L., PARTIDGE, M. R., WALTERS, E. H. & ZIELHUIS, G. A. 2007. Self-management education for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD002990.
- EISENBERG, M. J., FILION, K. B., YAVIN, D., BELISLE, P., MOTTILLO, S., JOSEPH, L., GERVAIS, A., O'LOUGHLIN, J., PARADIS, G., RINFRET, S. & PILOTE, L. 2008. Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. *CMAJ*, 179, 135-44.
- EISER, N., HARTE, R., SPIROS, K., PHILLIPS, C. & ISAAC, M. T. 2005. Effect of treating depression on quality-of-life and exercise tolerance in severe COPD. *COPD*, 2, 233-41.
- EISER, N., WILLSHER, D. & DORE, C. J. 2003. Reliability, repeatability and sensitivity to change of externally and self-paced walking tests in COPD patients. *Respir Med*, 97, 407-14.
- EISNER, M. D., ANTHONISEN, N., COULTAS, D., KUENZLI, N., PEREZ-PADILLA, R., POSTMA, D., ROMIEU, I., SILVERMAN, E. K. & BALMES, J. R. 2010a. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 182, 693-718.
- EISNER, M. D., BLANC, P. D., YELIN, E. H., KATZ, P. P., SANCHEZ, G., IRIBARREN, C. & OMACHI, T. A. 2010c. Influence of anxiety on health outcomes in COPD. *Thorax*, 65, 229-34.
- EKSTROM, M., FRANKLIN, K. A. & STROM, K. E. Increased relative mortality in women with severe oxygen-dependent COPD. *Chest*, 137, 31-6.
- EL MOUSSAOUI, R., ROEDE, B. M., SPEELMAN, P., BRESSER, P., PRINS, J. M. & BOSSUYT, P. M. 2008. Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. *Thorax*, 63, 415-22.
- ELLIOTT, M. W. 2002. Noninvasive ventilation in chronic ventilatory failure due to chronic obstructive pulmonary disease. *Eur Respir J*, 20, 511-4.
- ERNST, P., GONZALEZ, A. V., BRASSARD, P. & SUISSA, S. 2007. Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. *Am J Respir Crit Care Med*, 176, 162-6.
- ESTEBAN, A., ANZUETO, A., ALIA, I., GORDO, F., APEZTEGUIA, C., PALIZAS, F., CIDE, D., GOLDWASER, R., SOTO, L., BUGEDO, G., RODRIGO, C., PIMENTEL, J., RAIMONDI, G. & TOBIN, M. J. 2000. How is mechanical ventilation employed in the intensive care unit? An international utilization review. *Am J Respir Crit Care Med*, 161, 1450-8.
- ESTEBAN, C., QUINTANA, J. M., EGURROLA, M., MORAZA, J., ABURTO, M., PEREZ-IZQUIERDO, J., BASUALDO, L. V. & CAPELASTEGUI, A. 2009. Classifying the severity of COPD: are the new severity scales better than the old? *Int J Tuberc Lung Dis*, 13, 783-90.
- EURICH, D. T., SADOWSKI, C. A., SIMPSON, S. H., MARRIE, T. J. & MAJUMDAR, S. R. 2010. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *Am J Med*, 123, 47-53.
- EVANS, M., HAMMOND, M., WILSON, K., LYE, M. & COPELAND, J. 1997. Placebo-controlled treatment trial of depression in elderly physically ill patients. *Int J Geriatr Psychiatry*, 12, 817-24.
- EVANS, R. A., SINGH, S. J., COLLIER, R., WILLIAMS, J. E. & MORGAN, M. D. 2009. Pulmonary rehabilitation is successful for COPD irrespective of MRC dyspnoea grade. *Respir Med*, 103, 1070-5.

- FABBRI, L. M., CALVERLEY, P. M., IZQUIERDO-ALONSO, J. L., BUNDSCHUH, D. S., BROSE, M., MARTINEZ, F. J. & RABE, K. F. 2009. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet*, 374, 695-703.
- FALAGAS, M. E., AVGERI, S. G., MATTHAIIOU, D. K., DIMOPOULOS, G. & SIEMPOS, II 2008. Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis. *J Antimicrob Chemother*, 62, 442-50.
- FAN, V. S., GAZIANO, J. M., LEW, R., BOURBEAU, J., ADAMS, S. G., LEATHERMAN, S., THWIN, S. S., HUANG, G. D., ROBBINS, R., SRIRAM, P. S., SHARAFKHANEH, A., MADOR, M. J., SAROSI, G., PANOS, R. J., RASTOGI, P., WAGNER, T. H., MAZZUCA, S. A., SHANNON, C., COLLING, C., LIANG, M. H., STOLLER, J. K., FIORE, L. & NIEWOEHNER, D. E. 2012. A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial. *Ann Intern Med*, 156, 673-83.
- FEARY, J. R., RODRIGUES, L. C., SMITH, C. J., HUBBARD, R. B. & GIBSON, J. E. 2010. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax*, 65, 956-62.
- FERGUSON, G. T., CALVERLEY, P. M., ANDERSON, J. A., JENKINS, C. R., JONES, P. W., WILLITS, L. R., YATES, J. C., VESTBO, J. & CELLI, B. 2009. Prevalence and progression of osteoporosis in patients with COPD: results from the TOwards a Revolution in COPD Health study. *Chest*, 136, 1456-65.
- FERGUSON, G. T., FELDMAN, G. J., HOFBAUER, P., HAMILTON, A., ALLEN, L., KORDUCKI, L. & SACHS, P. 2014. Efficacy and safety of olodaterol once daily delivered via Respimat(R) in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *Int J Chron Obstruct Pulmon Dis*, 9, 629-45.
- FERNANDEZ, A., MUNOZ, J., DE LA CALLE, B., ALIA, I., EZPELETA, A., DE LA CAL, M. A. & REYES, A. 1994. Comparison of one versus two bronchodilators in ventilated COPD patients. *Intensive Care Med*, 20, 199-202.
- FERREIRA, I. M., BROOKS, D., WHITE, J. & GOLDSTEIN, R. 2012. Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 12, CD000998.
- FIORE, M. C., BAKER, T.B., BAILEY, W.C., BENOWITZ, N.L., CURRY, S.J., FOR THE GUIDELINE UPDATE PANEL 2008. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. *Respir Care*, 53, 1217-22.
- FISHMAN, A., MARTINEZ, F., NAUNHEIM, K., PIANTADOSI, S., WISE, R., RIES, A., WEINMANN, G. & WOOD, D. E. 2003. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med*, 348, 2059-73.
- FISHMAN, A. P. 1994. Pulmonary rehabilitation research. *Am J Respir Crit Care Med*, 149, 825-33.
- FLETCHER, C. & PETO, R. 1977. The natural history of chronic airflow obstruction. *Br Med J*, 1, 1645-8.
- FLETCHER, C. M., CLIFTON M., FAIRBAIRN AS., FRY J., GILSON JC., HIGGINS ITT., MAIR A., PEMBERTON J., ROGAN JM., SMITH DH. & WOOD CH. 1960. Standardized questionnaires on respiratory symptoms. *Br Med J*, 2, 1665.
- FOXWELL, A. R., CRIPPS, A. W. & DEAR, K. B. 2003. Haemophilus influenzae oral whole cell vaccination for preventing acute exacerbations of chronic bronchitis. *Cochrane Database Syst Rev*, CD001958.
- FURUMOTO, A., OHKUSA, Y., CHEN, M., KAWAKAMI, K., MASAKI, H., SUEYASU, Y., IWANAGA, T., AIZAWA, H., NAGATAKE, T. & OISHI, K. 2008. Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease. *Vaccine*, 26, 4284-9.
- FUSCHILLO, S., MARTUCCI, M., DONNER, C. F. & BALZANO, G. 2012. Airway bacterial colonization: the missing link between COPD and cardiovascular events? *Respir Med*, 106, 915-23.
- GAN, W. Q., MAN, S. F., POSTMA, D. S., CAMP, P. & SIN, D. D. 2006. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respir Res*, 7, 52.

- GARCIA-AYMERICH, J., LANGE, P., BENET, M., SCHNOHR, P. & ANTO, J. M. 2006. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax*, 61, 772-8.
- GARCIA-AYMERICH, J., SERRA, I., GOMEZ, F. P., FARRERO, E., BALCELLS, E., RODRIGUEZ, D. A., DE BATLLE, J., GIMENO, E., DONAIRE-GONZALEZ, D., OROZCO-LEVI, M., SAULEDA, J., GEA, J., RODRIGUEZ-ROISIN, R., ROCA, J., AGUSTI, A. G. & ANTO, J. M. 2009. Physical activity and clinical and functional status in COPD. *Chest*, 136, 62-70.
- GARCIA RODRIGUEZ, L. A., RUIGOMEZ, A., MARTIN-MERINO, E., JOHANSSON, S. & WALLANDER, M. A. 2008. Relationship between gastroesophageal reflux disease and COPD in UK primary care. *Chest*, 134, 1223-30.
- GEDDES, D., DAVIES, M., KOYAMA, H., HANSELL, D., PASTORINO, U., PEPPER, J., AGENT, P., CULLINAN, P., MACNEILL, S. J. & GOLDSTRAW, P. 2000. Effect of lung-volume-reduction surgery in patients with severe emphysema. *N Engl J Med*, 343, 239-45.
- GEELHOED, E. A., BRAMELD, K. J., HOLMAN, C. D. & THOMPSON, P. J. 2007. Readmission and survival following hospitalization for chronic obstructive pulmonary disease: long-term trends. *Intern Med J*, 37, 87-94.
- GIARDINO, N. D., CURTIS, J. L., ANDREI, A. C., FAN, V. S., BENDITT, J. O., LYUBKIN, M., NAUNHEIM, K., CRINER, G., MAKE, B., WISE, R. A., MURRAY, S. K., FISHMAN, A. P., SCIURBA, F. C., LIBERZON, I. & MARTINEZ, F. J. 2010. Anxiety is associated with diminished exercise performance and quality of life in severe emphysema: a cross-sectional study. *Respir Res*, 11, 29.
- GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE 2007. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2007).
- GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE 2009. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2009).
- GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD) 2006. Global Strategy for the Diagnosis, Management and Prevention of COPD.
- GOLD STANDARDS FRAMEWORK PROGRAMME 2005. Prognostic Indicator Paper Vs 2.25.
- GORE, J. M., BROPHY, C. J. & GREENSTONE, M. A. 2000. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax*, 55, 1000-6.
- GORECKA, D., GORZELAK, K., SLIWINSKI, P., TOBIASZ, M. & ZIELINSKI, J. 1997. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax*, 52, 674-9.
- GOSSELINK, R., DE VOS, J., VAN DEN HEUVEL, S. P., SEGERS, J., DECRAMER, M. & KWAKKEL, G. 2011. Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J*, 37, 416-25.
- GOTZSCHE, P. C. & JOHANSEN, H. K. 2010. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. *Cochrane Database Syst Rev*, CD007851.
- GOURLAY, S. G., STEAD, L. F. & BENOWITZ, N. L. 2004. Clonidine for smoking cessation. *Cochrane Database Syst Rev*, CD000058.
- GRAAT-VERBOOM, L., WOUTERS, E. F., SMEENK, F. W., VAN DEN BORNE, B. E., LUNDE, R. & SPRUIT, M. A. 2009. Current status of research on osteoporosis in COPD: a systematic review. *Eur Respir J*, 34, 209-18.
- GRANT, I., HEATON, R. K., MCSWEENEY, A. J., ADAMS, K. M. & TIMMS, R. M. 1982. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Arch Intern Med*, 142, 1470-6.
- GRIFFITHS, T. L., BURR, M. L., CAMPBELL, I. A., LEWIS-JENKINS, V., MULLINS, J., SHIELS, K., TURNER-LAWLOR, P. J., PAYNE, N., NEWCOMBE, R. G., IONESCU, A. A., THOMAS, J. & TUNBRIDGE, J. 2000. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet*, 355, 362-8.
- GRIFFITHS, T. L., PHILLIPS, C. J., DAVIES, S., BURR, M. L. & CAMPBELL, I. A. 2001. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax*, 56, 779-84.

- GROSS, N. J., PETTY, T. L., FRIEDMAN, M., SKORODIN, M. S., SILVERS, G. W. & DONOHUE, J. F. 1989. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-center study. *Am Rev Respir Dis*, 139, 1188-91.
- GROSS, R. D., ATWOOD, C. W., JR., ROSS, S. B., OLSZEWSKI, J. W. & EICHHORN, K. A. 2009. The coordination of breathing and swallowing in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 179, 559-65.
- GROSSMAN, J. M., GORDON, R., RANGANATH, V. K., DEAL, C., CAPLAN, L., CHEN, W., CURTIS, J. R., FURST, D. E., MCMAHON, M., PATKAR, N. M., VOLKMANN, E. & SAAG, K. G. 2010. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)*, 62, 1515-26.
- GUDMUNDSSON, G., GISLASON, T., JANSON, C., LINDBERG, E., HALLIN, R., ULRİK, C. S., BRONDUM, E., NIEMINEN, M. M., AINE, T. & BAKKE, P. 2005. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. *Eur Respir J*, 26, 414-9.
- GUDMUNDSSON, G., GISLASON, T., JANSON, C., LINDBERG, E., ULRİK, C. S., BRONDUM, E., NIEMINEN, M. M., AINE, T., HALLIN, R. & BAKKE, P. 2006. Depression, anxiety and health status after hospitalisation for COPD: A multicentre study in the Nordic countries. *Respiratory Medicine*, 100, 87-93.
- GULMEZ, S. E., HOLM, A., FREDERIKSEN, H., JENSEN, T. G., PEDERSEN, C. & HALLAS, J. 2007. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med*, 167, 950-5.
- GUNES, A., ABOYOUN, C. L., MORTON, J. M., PLIT, M., MALOUF, M. A. & GLANVILLE, A. R. 2006. Lung transplantation for chronic obstructive pulmonary disease at St Vincent's Hospital. *Intern Med J*, 36, 5-11.
- GUO, R., PITTLER, M. H. & ERNST, E. 2006. Herbal medicines for the treatment of COPD: a systematic review. *Eur Respir J*, 28, 330-8.
- GUPTA, D., AGARWAL, R., AGGARWAL, A. N., MATURU, V. N., DHOORIA, S., PRASAD, K. T., SEHGAL, I. S., YENGE, L. B., JINDAL, A., SINGH, N., GHOSHAL, A. G., KHILNANI, G. C., SAMARIA, J. K., GAUR, S. N., BEHERA, D. & JINDAL, S. K. 2014. Guidelines for diagnosis and management of chronic obstructive pulmonary disease: joint recommendations of Indian Chest Society and National College of Chest Physicians (India). *Indian J Chest Dis Allied Sci*, 56 Spec No, 5-54.
- GUYATT, G. H., TOWNSEND, M., PUGSLEY, S. O., KELLER, J. L., SHORT, H. D., TAYLOR, D. W. & NEWHOUSE, M. T. 1987. Bronchodilators in chronic air-flow limitation. Effects on airway function, exercise capacity, and quality of life. *Am Rev Respir Dis*, 135, 1069-74.
- HAJA MYDIN, H., MURPHY, S., CLAGUE, H., SRIDHARAN, K. & TAYLOR, I. K. 2013. Anemia and performance status as prognostic markers in acute hypercapnic respiratory failure due to chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*, 8, 151-7.
- HALPERN, M. T., ZILBERBERG, M. D., SCHMIER, J. K., LAU, E. C. & SHORR, A. F. 2006. Anemia, costs and mortality in chronic obstructive pulmonary disease. *Cost Eff Resour Alloc*, 4, 17.
- HAN, J., DAI, L. & ZHONG, N. 2013. Indacaterol on dyspnea in chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized placebo-controlled trials. *BMC Pulm Med*, 13, 26.
- HAN, M. K., TAYOB, N., MURRAY, S., DRANSFIELD, M. T., WASHKO, G., SCANLON, P. D., CRINER, G. J., CASABURI, R., CONNETT, J., LAZARUS, S. C., ALBERT, R., WOODRUFF, P. & MARTINEZ, F. J. 2014. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. *Am J Respir Crit Care Med*, 189, 1503-8.
- HANANIA, N. A., CRATER, G. D., MORRIS, A. N., EMMETT, A. H., O'DELL, D. M. & NIEWOEHNER, D. E. 2012. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. *Respir Med*, 106, 91-101.
- HANANIA, N. A., MULLEROVA, H., LOCANTORE, N. W., VESTBO, J., WATKINS, M. L., WOUTERS, E. F., RENNARD, S. I. & SHARAFKHANEH, A. 2011. Determinants of Depression in the ECLIPSE Chronic Obstructive Pulmonary Disease Cohort. *Am J Respir Crit Care Med*, 183, 604-611.

- HANSEL, N. N., MCCORMACK, M. C., BELLI, A. J., MATSUI, E. C., PENG, R. D., ALOE, C., PAULIN, L., WILLIAMS, D. L., DIETTE, G. B. & BREYSSE, P. N. 2013. In-home air pollution is linked to respiratory morbidity in former smokers with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 187, 1085-90.
- HARRISON, M. T., SHORT, P., WILLIAMSON, P. A., SINGANAYAGAM, A., CHALMERS, J. D. & SCHEMBRI, S. 2014. Thrombocytosis is associated with increased short and long term mortality after exacerbation of chronic obstructive pulmonary disease: a role for antiplatelet therapy? *Thorax*, 69, 609-15.
- HARRISON, S. L., GREENING, N. J., WILLIAMS, J. E., MORGAN, M. D., STEINER, M. C. & SINGH, S. J. 2012. Have we underestimated the efficacy of pulmonary rehabilitation in improving mood? *Respir Med*, 106, 838-44.
- HART, J. E., LADEN, F., EISEN, E. A., SMITH, T. J. & GARSHICK, E. 2009. Chronic obstructive pulmonary disease mortality in railroad workers. *Occup Environ Med*, 66, 221-6.
- HARTMANN-BOYCE, J., LANCASTER, T. & STEAD, L. F. 2014. Print-based self-help interventions for smoking cessation. *Cochrane Database Syst Rev*, 6, CD001118.
- HAY, J. G., STONE, P., CARTER, J., CHURCH, S., EYRE-BROOK, A., PEARSON, M. G., WOODCOCK, A. A. & CALVERLEY, P. M. 1992. Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. *Eur Respir J*, 5, 659-64.
- HERATH, S. C. & POOLE, P. 2013. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev*, 11, CD009764.
- HERNANDES, N. A., WOUTERS, E. F., MEIJER, K., ANNEGARN, J., PITTA, F. & SPRUIT, M. A. 2011. Reproducibility of 6-minute walking test in patients with COPD. *Eur Respir J*, 38, 261-7.
- HERTH, F. J., NOPPEN, M., VALIPOUR, A., LEROY, S., VERGNON, J. M., FICKER, J. H., EGAN, J. J., GASPARINI, S., AGUSTI, C., HOLMES-HIGGIN, D. & ERNST, A. 2012. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. *Eur Respir J*, 39, 1334-42.
- HIGGINS, B. G., POWELL, R. M., COOPER, S. & TATTERSFIELD, A. E. 1991. Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis. *Eur Respir J*, 4, 415-20.
- HILL, K., PATMAN, S. & BROOKS, D. 2010. Effect of airway clearance techniques in patients experiencing an acute exacerbation of chronic obstructive pulmonary disease: a systematic review. *Chron Respir Dis*, 7, 9-17.
- HOISETH, A. D., OMLAND, T., HAGVE, T. A., BREKKE, P. H. & SOYSETH, V. 2012. NT-proBNP independently predicts long term mortality after acute exacerbation of COPD - a prospective cohort study. *Respir Res*, 13, 97.
- HOLE, D. J., WATT, G. C., DAVEY-SMITH, G., HART, C. L., GILLIS, C. R. & HAWTHORNE, V. M. 1996. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ*, 313, 711-5; discussion 715-6.
- HOLGUIN, F., FOLCH, E., REDD, S. C. & MANNINO, D. M. 2005. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest*, 128, 2005-11.
- HOLLAND, A. E. & BUTTON, B. M. 2006. Is there a role for airway clearance techniques in chronic obstructive pulmonary disease? *Chron Respir Dis*, 3, 83-91.
- HOLLAND, A. E., HILL, C. J., JONES, A. Y. & MCDONALD, C. F. 2012. Breathing exercises for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 10, CD008250.
- HOLVERDA, S., RIETEMA, H., BOGAARD, H. J., WESTERHOF, N., POSTMUS, P. E., BOONSTRA, A. & VONK-NOORDEGRAAF, A. 2008. Acute effects of sildenafil on exercise pulmonary hemodynamics and capacity in patients with COPD. *Pulm Pharmacol Ther*, 21, 558-64.
- HOMIK, J., CRANNEY, A., SHEA, B., TUGWELL, P., WELLS, G., ADACHI, R. & SUAREZ-ALMAZOR, M. 2000. Bisphosphonates for steroid induced osteoporosis. *Cochrane Database Syst Rev*, CD001347.
- HOOGENDOORN, M., FEENSTRA, T. L., HOOGENVEEN, R. T., AL, M. & MOLKEN, M. R. 2010a. Association between lung function and exacerbation frequency in patients with COPD. *Int J Chron Obstruct Pulmon Dis*, 5, 435-44.
- HOOGENDOORN, M., FEENSTRA, T. L., HOOGENVEEN, R. T. & RUTTEN-VAN MOLKEN, M. P. 2010b. Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. *Thorax*, 65, 711-8.

- HOOGENDOORN, M., HOOGENVEEN, R. T., RUTTEN-VAN MOLKEN, M. P., VESTBO, J. & FEENSTRA, T. L. 2010c. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. *Eur Respir J*, 37, 508-15.
- HORITA, N., MIYAZAWA, N., KOJIMA, R., INOUE, M., ISHIGATSUBO, Y., UEDA, A. & KANEKO, T. 2014. Statins reduce all-cause mortality in chronic obstructive pulmonary disease: a systematic review and meta-analysis of observational studies. *Respir Res*, 15, 80.
- HORNIKX, M., VAN REMOORTEL, H., LEHOUCQ, A., MATHIEU, C., MAES, K., GAYAN-RAMIREZ, G., DECRAMER, M., TROOSTERS, T. & JANSSENS, W. 2012. Vitamin D supplementation during rehabilitation in COPD: a secondary analysis of a randomized trial. *Respir Res*, 13, 84.
- HU, G., ZHOU, Y., TIAN, J., YAO, W., LI, J., LI, B. & RAN, P. 2010. Risk of COPD from exposure to biomass smoke: a metaanalysis. *Chest*, 138, 20-31.
- HUGHES, J. R., STEAD, L. F., HARTMANN-BOYCE, J., CAHILL, K. & LANCASTER, T. 2014. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*, 1, CD000031.
- HUGHES, J. R., STEAD, L. F. & LANCASTER, T. 2000. Anxiolytics for smoking cessation. *Cochrane Database Syst Rev*, CD002849.
- HUGHES, J. R., STEAD, L. F. & LANCASTER, T. 2007. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*, CD000031.
- HUNG, W. W., WISNIVESKY, J. P., SIU, A. L. & ROSS, J. S. 2009. Cognitive decline among patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 180, 134-7.
- HUNTER, C. J., BRIGHTLING, C. E., WOLTMANN, G., WARDLAW, A. J. & PAVORD, I. D. 2002. A comparison of the validity of different diagnostic tests in adults with asthma. *Chest*, 121, 1051-7.
- HURST, J. R., VESTBO, J., ANZUETO, A., LOCANTORE, N., MULLEROVA, H., TAL-SINGER, R., MILLER, B., LOMAS, D. A., AGUSTI, A., MACNEE, W., CALVERLEY, P., RENNARD, S., WOUTERS, E. F. & WEDZICHA, J. A. 2010. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*, 363, 1128-38.
- HYNNINEN, M. J., BJERKE, N., PALLESEN, S., BAKKE, P. S. & NORDHUS, I. H. 2010. A randomized controlled trial of cognitive behavioral therapy for anxiety and depression in COPD. *Respir Med*, 104, 986-94.
- INCALZI, R. A., GEMMA, A., MARRA, C., CAPPARELLA, O., FUSO, L. & CARBONIN, P. 1997. Verbal memory impairment in COPD: its mechanisms and clinical relevance. *Chest*, 112, 1506-13.
- ISADA CM & STOLLER JK 1994. Chronic bronchitis: the role of antibiotics. In: NIEDERMAN MS, SAROSI GA & GLASSROTH J (eds.) *Respiratory Infections: a Scientific Basis for Management*. London: WB Saunders.
- IVERSEN, K. K., KJAERGAARD, J., AKKAN, D., KOBER, L., TORP-PEDERSEN, C., HASSAGER, C., VESTBO, J. & KJOLLER, E. 2008. Chronic obstructive pulmonary disease in patients admitted with heart failure. *J Intern Med*, 264, 361-9.
- IYER, A. S., WELLS, J. M., VISHIN, S., BHATT, S. P., WILLE, K. M. & DRANSFIELD, M. T. 2014. CT scan-measured pulmonary artery to aorta ratio and echocardiography for detecting pulmonary hypertension in severe COPD. *Chest*, 145, 824-32.
- JANDA, S., PARK, K., FITZGERALD, J. M., ETMINAN, M. & SWISTON, J. 2009. Statins in COPD: a systematic review. *Chest*, 136, 734-43.
- JANSSEN, D. J., SPRUIT, M. A., SCHOLS, J. M., COX, B., NAWROT, T. S., CURTIS, J. R. & WOUTERS, E. F. 2012. Predicting changes in preferences for life-sustaining treatment among patients with advanced chronic organ failure. *Chest*, 141, 1251-9.
- JENKINS, C. R., CELLI, B., ANDERSON, J. A., FERGUSON, G. T., JONES, P. W., VESTBO, J., YATES, J. C. & CALVERLEY, P. M. 2012. Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *Eur Respir J*, 39, 38-45.
- JENKINS, S. A. C., N 2011. Do all patients with COPD attending pulmonary rehabilitation need a practice 6-minute walk test (6MWT)? *Respirology*, 16, 37-86.
- JENKINS, S. C., HEATON, R. W., FULTON, T. J. & MOXHAM, J. 1987. Comparison of domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. *Chest*, 91, 804-7.

- JENNINGS, A. L., DAVIES, A. N., HIGGINS, J. P., GIBBS, J. S. & BROADLEY, K. E. 2002. A systematic review of the use of opioids in the management of dyspnoea. *Thorax*, 57, 939-44.
- JEPPESEN, E., BRURBERG, K. G., VIST, G. E., WEDZICHA, J. A., WRIGHT, J. J., GREENSTONE, M. & WALTERS, J. A. 2012. Hospital at home for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 5, CD003573.
- JIANG, F. M., LIANG, Z. A., ZHENG, Q. L., WANG, R. C., LUO, J. & LI, C. T. 2013. Safety and efficacy of 12-week or longer indacaterol treatment in moderate-to-severe COPD patients: a systematic review. *Lung*, 191, 135-46.
- JONES, A., FAY, J. K., BURR, M., STONE, M., HOOD, K. & ROBERTS, G. 2002. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD003537.
- JONES, A. T. & EVANS, T. W. 1997. NO: COPD and beyond. *Thorax*, 52 Suppl 3, S16-21.
- JONES, D. A. & PETERS, T. J. 1992. Caring for elderly dependents: effects on the carers' quality of life. *Age Ageing*, 21, 421-8.
- JONES, P. W., ANDERSON, J. A., CALVERLEY, P. M., CELLI, B. R., FERGUSON, G. T., JENKINS, C., YATES, J. C., VESTBO, J. & SPENCER, M. D. 2011a. Health status in the TORCH study of COPD: treatment efficacy and other determinants of change. *Respir Res*, 12, 71.
- JONES, P. W., HARDING, G., BERRY, P., WIKLUND, I., CHEN, W. H. & KLINE LEIDY, N. 2009. Development and first validation of the COPD Assessment Test. *Eur Respir J*, 34, 648-54.
- JONES, P. W., MAHLER, D. A., GALE, R., OWEN, R. & KRAMER, B. 2011b. Profiling the effects of indacaterol on dyspnoea and health status in patients with COPD. *Respir Med*, 105, 892-9.
- JONES, P. W., SINGH, D., BATEMAN, E. D., AGUSTI, A., LAMARCA, R., DE MIQUEL, G., SEGARRA, R., CARACTA, C. & GARCIA GIL, E. 2012. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J*, 40, 830-6.
- JORDAN, N., LEE, T. A., VALENSTEIN, M., PIRRAGLIA, P. A. & WEISS, K. B. 2009. Effect of depression care on outcomes in COPD patients with depression. *Chest*, 135, 626-32.
- JOSEPH, A. M., NORMAN, S. M., FERRY, L. H., PROCHAZKA, A. V., WESTMAN, E. C., STEELE, B. G., SHERMAN, S. E., CLEVELAND, M., ANTONUCCIO, D. O., HARTMAN, N. & MCGOVERN, P. G. 1996. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med*, 335, 1792-8.
- JUNG, K. S., PARK, H. Y., PARK, S. Y., KIM, S. K., KIM, Y. K., SHIM, J. J., MOON, H. S., LEE, K. H., YOO, J. H. & LEE, S. D. 2012. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. *Respir Med*, 106, 382-9.
- KARABIS, A., LINDNER, L., MOCARSKI, M., HUISMAN, E. & GREENING, A. 2013. Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. *Int J Chron Obstruct Pulmon Dis*, 8, 405-23.
- KARDOS, P., WENCKER, M., GLAAB, T. & VOGELMEIER, C. 2007. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 175, 144-9.
- KARNER, C. & CATES, C. J. 2011. Combination inhaled steroid and long-acting beta(2)-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD008532.
- KARNER, C. & CATES, C. J. 2012. Long-acting beta(2)-agonist in addition to tiotropium versus either tiotropium or long-acting beta(2)-agonist alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 4, CD008989.
- KARNER, C., CHONG, J. & POOLE, P. 2014. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 7, CD009285.
- KASTELIK, J. A., LOWE, D., STONE, R. A., BUCKINGHAM, R. J. & ROBERTS, C. M. 2012. National audit of supported discharge programmes for management of acute exacerbations of chronic obstructive pulmonary disease 2008. *Thorax*, 67, 371-3.
- KATON, W., LIN, E. H. & KROENKE, K. 2007. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry*, 29, 147-55.

- KELLY, C. A. & GIBSON, G. J. 1988. Relation between FEV1 and peak expiratory flow in patients with chronic airflow obstruction. *Thorax*, 43, 335-6.
- KENNEDY, A., REEVES, D., BOWER, P., LEE, V., MIDDLETON, E., RICHARDSON, G., GARDNER, C., GATELY, C. & ROGERS, A. 2007. The effectiveness and cost effectiveness of a national lay-led self care support programme for patients with long-term conditions: a pragmatic randomised controlled trial. *J Epidemiol Community Health*, 61, 254-61.
- KERANIS, E., MAKRIS, D., RODOPOULOU, P., MARTINO, H., PAPAMAKARIOS, G., DANIIL, Z., ZINTZARAS, E. & GOURGOULIANIS, K. I. 2010. Impact of dietary shift to higher-antioxidant foods in COPD: a randomised trial. *Eur Respir J*, 36, 774-80.
- KERWIN, E., HEBERT, J., GALLAGHER, N., MARTIN, C., OVEREND, T., ALAGAPPAN, V. K., LU, Y. & BANERJI, D. 2012. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. *Eur Respir J*, 40, 1106-14.
- KERWIN, E. M., SCOTT-WILSON, C., SANFORD, L., RENNARD, S., AGUSTI, A., BARNES, N. & CRIM, C. 2013. A randomised trial of fluticasone furoate/vilanterol (50/25 mug; 100/25 mug) on lung function in COPD. *Respir Med*, 107, 560-9.
- KESSLER, R., FALLER, M., FOURGAUT, G., MENNECIER, B. & WEITZENBLUM, E. 1999. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 159, 158-64.
- KESTEN, S., JARA, M., WENTWORTH, C. & LANES, S. 2006. Pooled clinical trial analysis of tiotropium safety. *Chest*, 130, 1695-703.
- KEW, K. M., DIAS, S. & CATES, C. J. 2014. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database Syst Rev*, 3, CD010844.
- KEW, K. M., MAVERGAMES, C. & WALTERS, J. A. 2013. Long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 10, CD010177.
- KEW, K. M. & SENIUKOVICH, A. 2014. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 3, CD010115.
- KLIBER, A., LYND, L. D. & SIN, D. D. 2010. The effects of long-acting bronchodilators on total mortality in patients with stable chronic obstructive pulmonary disease. *Respir Res*, 11, 56.
- KOBAYASHI, M., NASUHARA, Y., BETSUYAKU, T., SHIBUYA, E., TANINO, Y., TANINO, M., TAKAMURA, K., NAGAI, K., HOSOKAWA, T. & NISHIMURA, M. 2004. Effect of low-dose theophylline on airway inflammation in COPD. *Respirology*, 9, 249-54.
- KOCH, A., PIZZICHINI, E., HAMILTON, A., HART, L., KORDUCKI, L., DE SALVO, M. C. & PAGGIARO, P. 2014. Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat(R) versus placebo and formoterol twice daily in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *Int J Chron Obstruct Pulmon Dis*, 9, 697-714.
- KOHNLEIN, T., WINDISCH, W., KOHLER, D., DRABIK, A., GEISELER, J., HARTL, S., KARG, O., LAIER-GROENEVELD, G., NAVA, S., SCHONHOFER, B., SCHUCHER, B., WEGSCHEIDER, K., CRIE, C. P. & WELTE, T. 2014. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med*, 2, 698-705.
- KOLLERT, F., TIPPELT, A., MULLER, C., JORRES, R. A., PORZELIUS, C., PFEIFER, M. & BUDWEISER, S. 2013. Hemoglobin levels above anemia thresholds are maximally predictive for long-term survival in COPD with chronic respiratory failure. *Respir Care*, 58, 1204-12.
- KOLODZIEJ, M. A., JENSEN, L., ROWE, B. & SIN, D. 2007. Systematic review of noninvasive positive pressure ventilation in severe stable COPD. *Eur Respir J*, 30, 293-306.
- KONECNY, T., PARK, J. Y., SOMERS, K. R., KONECNY, D., ORBAN, M., SOUCEK, F., PARKER, K. O., SCANLON, P. D., ASIRVATHAM, S. J., BRADY, P. A. & RIHAL, C. S. 2014. Relation of chronic obstructive pulmonary disease to atrial and ventricular arrhythmias. *Am J Cardiol*, 114, 272-7.
- KONECNY, T., SOMERS, K., ORBAN, M., KOSHINO, Y., LENNON, R. J., SCANLON, P. D. & RIHAL, C. S. 2010. Interactions between COPD and outcomes after percutaneous coronary intervention. *Chest*, 138, 621-7.

- KONG, G. K., BELMAN, M. J. & WEINGARTEN, S. 1997. Reducing length of stay for patients hospitalized with exacerbation of COPD by using a practice guideline. *Chest*, 111, 89-94.
- KORNMAN, O., DAHL, R., CENTANNI, S., DOGRA, A., OWEN, R., LASSEN, C. & KRAMER, B. 2011. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. *Eur Respir J*, 37, 273-9.
- KORNUM, J. B., SVAERKE, C., THOMSEN, R. W., LANGE, P. & SORENSEN, H. T. 2012. Chronic obstructive pulmonary disease and cancer risk: a Danish nationwide cohort study. *Respir Med*, 106, 845-52.
- KOTTKE, T. E., BATTISTA, R. N., DEFRIESE, G. H. & BREKKE, M. L. 1988. Attributes of successful smoking cessation interventions in medical practice. A meta-analysis of 39 controlled trials. *JAMA*, 259, 2883-9.
- KRAMER, N., MEYER, T. J., MEHARG, J., CECE, R. D. & HILL, N. S. 1995. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med*, 151, 1799-806.
- KRISHNAN, G., GRANT, B. J., MUTI, P. C., MISHRA, A., OCHS-BALCOM, H. M., FREUDENHEIM, J. L., TREVISAN, M. & SCHUNEMANN, H. J. 2006. Association between anemia and quality of life in a population sample of individuals with chronic obstructive pulmonary disease. *BMC Pulm Med*, 6, 23.
- KRUIS, A. L., SMIDT, N., ASSENDELFT, W. J., GUSSEKLOO, J., BOLAND, M. R., RUTTEN-VAN MOLKEN, M. & CHAVANNES, N. H. 2013. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 10, CD009437.
- KUNIK, M. E., BRAUN, U., STANLEY, M. A., WRISTERS, K., MOLINARI, V., STOEBCNER, D. & ORENGO, C. A. 2001. One session cognitive behavioural therapy for elderly patients with chronic obstructive pulmonary disease. *Psychol Med*, 31, 717-23.
- KUNIK, M. E., ROUNDY, K., VEAZEY, C., SOUCHEK, J., RICHARDSON, P., WRAY, N. P. & STANLEY, M. A. 2005. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. *Chest*, 127, 1205-11.
- LACASSE, Y., BEAUDOIN, L., ROUSSEAU, L. & MALTAIS, F. 2004. Randomized trial of paroxetine in end-stage COPD. *Monaldi Arch Chest Dis*, 61, 140-7.
- LACASSE, Y., GOLDSTEIN, R., LASSERSON, T. J. & MARTIN, S. 2006. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD003793.
- LAHOUSSE, L., VAN DEN BOUWHUIJSEN, Q. J., LOTH, D. W., JOOS, G. F., HOFMAN, A., WITTEMAN, J. C., VAN DER LUGT, A., BRUSSELLE, G. G. & STRICKER, B. H. 2013. Chronic obstructive pulmonary disease and lipid core carotid artery plaques in the elderly: the Rotterdam Study. *Am J Respir Crit Care Med*, 187, 58-64.
- LANCASTER, T. & STEAD, L. 2004. Physician advice for smoking cessation. *Cochrane Database Syst Rev*, CD000165.
- LANCASTER, T., STEAD, L., SILAGY, C. & SOWDEN, A. 2000. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ*, 321, 355-8.
- LANCASTER, T. & STEAD, L. F. 2005. Individual behavioural counselling for smoking cessation. *Cochrane Database Syst Rev*, CD001292.
- LANDBO, C., PRESCOTT, E., LANGE, P., VESTBO, J. & ALMDAL, T. P. 1999. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 160, 1856-61.
- LANGE, N. E., SPARROW, D., VOKONAS, P. & LITONJUA, A. A. 2012. Vitamin D deficiency, smoking, and lung function in the Normative Aging Study. *Am J Respir Crit Care Med*, 186, 616-21.
- LAROS, C. D., GELISSEN, H. J., BERGSTEIN, P. G., VAN DEN BOSCH, J. M., VANDERSCHUEREN, R. G., WESTERMANN, C. J. & KNAEPEN, P. J. 1986. Bullectomy for giant bullae in emphysema. *J Thorac Cardiovasc Surg*, 91, 63-70.
- LAURIN, C., LABRECQUE, M., DUPUIS, G., BACON, S. L., CARTIER, A. & LAVOIE, K. L. 2009. Chronic obstructive pulmonary disease patients with psychiatric disorders are at greater risk of exacerbations. *Psychosom Med*, 71, 667-74.
- LAURIN, C., LAVOIE, K. L., BACON, S. L., DUPUIS, G., LACOSTE, G., CARTIER, A. & LABRECQUE, M. 2007. Sex differences in the prevalence of psychiatric disorders and psychological distress in patients with COPD. *Chest*, 132, 148-55.

- LAURIN, C., MOULLEC, G., BACON, S. L. & LAVOIE, K. L. 2012. Impact of anxiety and depression on chronic obstructive pulmonary disease exacerbation risk. *Am J Respir Crit Care Med*, 185, 918-23.
- LAVIOLETTE, L., LANDS, L. C., DAULETBAEV, N., SAEY, D., MILOT, J., PROVENCHER, S., LEBLANC, P. & MALTAIS, F. 2010. Combined effect of dietary supplementation with pressurized whey and exercise training in chronic obstructive pulmonary disease: a randomized, controlled, double-blind pilot study. *J Med Food*, 13, 589-98.
- LAWES, C. M., THORNLEY, S., YOUNG, R., HOPKINS, R., MARSHALL, R., CHAN, W. C. & JACKSON, G. 2012. Statin use in COPD patients is associated with a reduction in mortality: a national cohort study. *Prim Care Respir J*, 21, 35-40.
- LEE, P. N. & FRY, J. S. 2010. Systematic review of the evidence relating FEV1 decline to giving up smoking. *BMC Med*, 8, 84.
- LEE, T. A., PICKARD, A. S., AU, D. H., BARTLE, B. & WEISS, K. B. 2008. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med*, 149, 380-90.
- LEE, T. A., WILKE, C., JOO, M., STROUPE, K. T., KRISHNAN, J. A., SCHUMOCK, G. T. & PICKARD, A. S. 2009. Outcomes associated with tiotropium use in patients with chronic obstructive pulmonary disease. *Arch Intern Med*, 169, 1403-10.
- LEHOUCQ, A., MATHIEU, C., CARREMANS, C., BAEKE, F., VERHAEGEN, J., VAN ELDERE, J., DECALLONNE, B., BOUILLON, R., DECRAMER, M. & JANSSENS, W. 2012. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*, 156, 105-14.
- LEUPPI, J. D., SCHUETZ, P., BINGISSER, R., BODMER, M., BRIEL, M., DRESCHER, T., DUERRING, U., HENZEN, C., LEIBBRANDT, Y., MAIER, S., MIEDINGER, D., MULLER, B., SCHERR, A., SCHINDLER, C., STOECKLI, R., VIATTE, S., VON GARNIER, C., TAMM, M. & RUTISHAUSER, J. 2013. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA*, 309, 2223-31.
- LI, L. S., CAUGHEY, G. E. & JOHNSTON, K. N. 2014. The association between co-morbidities and physical performance in people with chronic obstructive pulmonary disease: a systematic review. *Chron Respir Dis*, 11, 3-13.
- LINDENAUER, P. K., PEKOW, P. S., LAHTI, M. C., LEE, Y., BENJAMIN, E. M. & ROTHBERG, M. B. 2010. Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. *JAMA*, 303, 2359-67.
- LINDSON, N., AVEYARD, P. & HUGHES, J. R. 2010. Reduction versus abrupt cessation in smokers who want to quit. *Cochrane Database Syst Rev*, CD008033.
- LIVERMORE, N., SHARPE, L. & MCKENZIE, D. 2010. Prevention of panic attacks and panic disorder in COPD. *Eur Respir J*, 35, 557-63.
- LORIG, K. R., SOBEL, D. S., STEWART, A. L., BROWN, B. W., JR., BANDURA, A., RITTER, P., GONZALEZ, V. M., LAURENT, D. D. & HOLMAN, H. R. 1999. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. *Med Care*, 37, 5-14.
- LUCAS, A. E., SMEENK, F. J., SMEELE, I. J. & VAN SCHAYCK, O. P. 2012. Diagnostic accuracy of primary care asthma/COPD working hypotheses, a real life study. *Respir Med*, 106, 1158-63.
- LUNG HEALTH STUDY RESEARCH GROUP 2000. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med*, 343, 1902-9.
- MACFARLANE, J. T., COLVILLE, A., GUION, A., MACFARLANE, R. M. & ROSE, D. H. 1993. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet*, 341, 511-4.
- MACLAY, J. D., MCALLISTER, D. A., MILLS, N. L., PATERSON, F. P., LUDLAM, C. A., DROST, E. M., NEWBY, D. E. & MACNEE, W. 2009. Vascular dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 180, 513-20.
- MAGNUSSEN, H., WATZ, H., KIRSTEN, A., DECRAMER, M., DAHL, R., CALVERLEY, P. M., TOWSE, L., FINNIGAN, H., TETZLAFF, K. & DISSE, B. 2014. Stepwise withdrawal of inhaled

- corticosteroids in COPD patients receiving dual bronchodilation: WISDOM study design and rationale. *Respir Med*, 108, 593-9.
- MAHMARIAN, J. J., MOYE, L. A., NASSER, G. A., NAGUEH, S. F., BLOOM, M. F., BENOWITZ, N. L., VERANI, M. S., BYRD, W. G. & PRATT, C. M. 1997. Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischemia. *J Am Coll Cardiol*, 30, 125-30.
- MAINGUY, V., GIRARD, D., MALTAIS, F., SAEY, D., MILOT, J., SENECHAL, M., POIRIER, P. & PROVENCHER, S. 2012. Effect of bisoprolol on respiratory function and exercise capacity in chronic obstructive pulmonary disease. *Am J Cardiol*, 110, 258-63.
- MALTAIS, F., CELLI, B., CASABURI, R., PORZASZ, J., JARRETA, D., SEOANE, B. & CARACTA, C. 2011. Acridinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. *Respir Med*, 105, 580-7.
- MARCHETTI, N., GARSHICK, E., KINNEY, G. L., MCKENZIE, A., STINSON, D., LUTZ, S. M., LYNCH, D. A., CRINER, G. J., SILVERMAN, E. K. & CRAPO, J. D. 2014. Association between occupational exposure and lung function, respiratory symptoms, and high-resolution computed tomography imaging in COPDGene. *Am J Respir Crit Care Med*, 190, 756-62.
- MARIN, J. M., SORIANO, J. B., CARRIZO, S. J., BOLDOVA, A. & CELLI, B. R. 2010. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med*, 182, 325-31.
- MARKOULAKI, D., KOSTIKAS, K., PAPATHEODOROU, G., KOUTSOKERA, A., ALCHANATIS, M., BAKAKOS, P., GOURGOULIANIS, K. I., ROUSSOS, C., KOULOURIS, N. G. & LOUKIDES, S. 2011. Hemoglobin, erythropoietin and systemic inflammation in exacerbations of chronic obstructive pulmonary disease. *Eur J Intern Med*, 22, 103-7.
- MARSH, S. E., TRAVERS, J., WEATHERALL, M., WILLIAMS, M. V., ALDINGTON, S., SHIRTCLIFFE, P. M., HANSELL, A. L., NOWITZ, M. R., MCNAUGHTON, A. A., SORIANO, J. B. & BEASLEY, R. W. 2008. Proportional classifications of COPD phenotypes. *Thorax*, 63, 761-7.
- MARTINEZ-RIVERA, C., PORTILLO, K., MUNOZ-FERRER, A., MARTINEZ-ORTIZ, M. L., MOLINS, E., SERRA, P., RUIZ-MANZANO, J. & MORERA, J. 2012. Anemia is a mortality predictor in hospitalized patients for COPD exacerbation. *COPD*, 9, 243-50.
- MARTINEZ, C. H., OKAJIMA, Y., MURRAY, S., WASHKO, G. R., MARTINEZ, F. J., SILVERMAN, E. K., LEE, J. H., REGAN, E. A., CRAPO, J. D., CURTIS, J. L., HATABU, H. & HAN, M. K. 2014. Impact of self-reported gastroesophageal reflux disease in subjects from COPDGene cohort. *Respir Res*, 15, 62.
- MARTINEZ, F. J., BOSCHIA, J., FELDMAN, G., SCOTT-WILSON, C., KILBRIDE, S., FABBRI, L., CRIM, C. & CALVERLEY, P. M. 2013. Fluticasone furoate/vilanterol (100/25; 200/25 mug) improves lung function in COPD: a randomised trial. *Respir Med*, 107, 550-9.
- MATHERS, C., VOS, T. & STEVENSON, C. 1999. *The Burden of Disease and Injury in Australia*, Canberra, Australian Institute of Health and Welfare.
- MATHESON, M. C., BENKE, G., RAVEN, J., SIM, M. R., KROMHOUT, H., VERMEULEN, R., JOHNS, D. P., WALTERS, E. H. & ABRAMSON, M. J. 2005. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. *Thorax*, 60, 645-51.
- MCCORD, J. & BORZAK, S. 1998. Multifocal atrial tachycardia. *Chest*, 113, 203-9.
- MCDONALD, C. F., CROCKETT, A. J. & YOUNG, I. H. 2005. Adult domiciliary oxygen therapy. Position statement of the Thoracic Society of Australia and New Zealand. *Med J Aust*, 182, 621-6.
- MCEVOY, R. D., PIERCE, R. J., HILLMAN, D., ESTERMAN, A., ELLIS, E. E., CATCHESIDE, P. G., O'DONOGHUE, F. J., BARNES, D. J. & GRUNSTEIN, R. R. 2009. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax*, 64, 561-6.
- MCKAY, S. E., HOWIE, C. A., THOMSON, A. H., WHITING, B. & ADDIS, G. J. 1993. Value of theophylline treatment in patients handicapped by chronic obstructive lung disease. *Thorax*, 48, 227-32.
- MCKEOUGH, Z. J., LEUNG, R. W. & ALISON, J. A. 2011. Shuttle walk tests as outcome measures: Are two incremental shuttle walk tests and two endurance shuttle walk tests necessary? *Am J Phys Med Rehabil*, 90, 35-9.
- MCLEAN, S., NURMATOV, U., LIU, J. L., PAGLIARI, C., CAR, J. & SHEIKH, A. 2011. Telehealthcare for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD007718.

- MCNAMARA, R. J., MCKEOUGH, Z. J., MCKENZIE, D. K. & ALISON, J. A. 2013. Water-based exercise training for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 12, CD008290.
- MCNICHOLAS, W. T. 2009. Chronic obstructive pulmonary disease and obstructive sleep apnea: overlaps in pathophysiology, systemic inflammation, and cardiovascular disease. *Am J Respir Crit Care Med*, 180, 692-700.
- MEDICAL RESEARCH COUNCIL WORKING PARTY 1981. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet*, 1, 681-6.
- MEECHAM JONES, D. J., PAUL, E. A., JONES, P. W. & WEDZICHA, J. A. 1995. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *Am J Respir Crit Care Med*, 152, 538-44.
- MEHRAN, R. J. & DESLAURIERS, J. 1995. Indications for surgery and patient work-up for bullectomy. *Chest Surg Clin N Am*, 5, 717-34.
- MEHTA, A. J., MIEDINGER, D., KEIDEL, D., BETTSCHART, R., BIRCHER, A., BRIDEVAUX, P. O., CURJURIC, I., KROMHOUT, H., ROCHAT, T., ROTHE, T., RUSSI, E. W., SCHIKOWSKI, T., SCHINDLER, C., SCHWARTZ, J., TURK, A., VERMEULEN, R., PROBST-HENSCH, N. & KUNZLI, N. 2012. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. *Am J Respir Crit Care Med*, 185, 1292-300.
- MEINE, T. J., PATEL, M. R., WASHAM, J. B., PAPPAS, P. A. & JOLLIS, J. G. 2005. Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. *Am J Cardiol*, 95, 976-8.
- MELANI, A. S., BONAVIDA, M., CILENTI, V., CINTI, C., LODI, M., MARTUCCI, P., SERRA, M., SCICCHILONE, N., SESTINI, P., ALIANI, M. & NERI, M. 2011. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med*, 105, 930-8.
- MENTZ, R. J., WOJDYLA, D., FIUZAT, M., CHISWELL, K., FONAROW, G. C. & O'CONNOR, C. M. 2013. Association of beta-blocker use and selectivity with outcomes in patients with heart failure and chronic obstructive pulmonary disease (from OPTIMIZE-HF). *Am J Cardiol*, 111, 582-7.
- MERCER, S. W., SMITH, S. M., WYKE, S., O'DOWD, T. & WATT, G. C. 2009. Multimorbidity in primary care: developing the research agenda. *Fam Pract*, 26, 79-80.
- MEYER, T. J. & HILL, N. S. 1994. Noninvasive positive pressure ventilation to treat respiratory failure. *Ann Intern Med*, 120, 760-70.
- MILLER, M. R., HANKINSON, J., BRUSASCO, V., BURGOS, F., CASABURI, R., COATES, A., CRAPO, R., ENRIGHT, P., VAN DER GRINTEN, C. P., GUSTAFSSON, P., JENSEN, R., JOHNSON, D. C., MACINTYRE, N., MCKAY, R., NAVAJAS, D., PEDERSEN, O. F., PELLEGRINO, R., VIEGI, G. & WANGER, J. 2005. Standardisation of spirometry. *Eur Respir J*, 26, 319-38.
- MIMS AUSTRALIA PTY LTD. 2008. *MIMS Online* [Online]. Sydney: Health Communication Network. Available: <http://www.mims.com.au>.
- MINISTRY OF HEALTH 2010. Mortality and Demographic Data 2007. Wellington: Ministry of Health.
- MIRAVITLLES, M., ESPINOSA, C., FERNANDEZ-LASO, E., MARTOS, J. A., MALDONADO, J. A. & GALLEGU, M. 1999. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Study Group of Bacterial Infection in COPD. *Chest*, 116, 40-6.
- MIRAVITLLES, M., FERRER, M., PONT, A., ZALACAIN, R., ALVAREZ-SALA, J. L., MASA, F., VERA, H., MURIO, C., ROS, F. & VIDAL, R. 2004. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. *Thorax*, 59, 387-95.
- MIRAVITLLES, M., MORAGAS, A., HERNANDEZ, S., BAYONA, C. & LLOR, C. 2013. Is it possible to identify exacerbations of mild to moderate COPD that do not require antibiotic treatment? *Chest*, 144, 1571-7.
- MITTE, K. 2005. A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. *J Affect Disord*, 88, 27-45.

- MOAYYEDI, P., CONGLETON, J., PAGE, R. L., PEARSON, S. B. & MUERS, M. F. 1995. Comparison of nebulised salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. *Thorax*, 50, 834-7.
- MOGULKOC, N., KARAKURT, S., ISALSKA, B., BAYINDIR, U., CELIKEL, T., KORTEN, V. & COLPAN, N. 1999. Acute purulent exacerbation of chronic obstructive pulmonary disease and Chlamydia pneumoniae infection. *Am J Respir Crit Care Med*, 160, 349-53.
- MOLFINO, N. A. & ZHANG, P. 2006. A meta-analysis on the efficacy of oral theophylline in patients with stable COPD. *Int J Chron Obstruct Pulmon Dis*, 1, 261-6.
- MONTERO, M., DOMINGUEZ, M., OROZCO-LEVI, M., SALVADO, M. & KNOBEL, H. 2009. Mortality of COPD patients infected with multi-resistant Pseudomonas aeruginosa: a case and control study. *Infection*, 37, 16-9.
- MOORE, R. P., BERLOWITZ, D. J., DENEHY, L., PRETTO, J. J., BRAZZALE, D. J., SHARPE, K., JACKSON, B. & MCDONALD, C. F. 2011. A randomised trial of domiciliary, ambulatory oxygen in patients with COPD and dyspnoea but without resting hypoxaemia. *Thorax*, 66, 32-7.
- MORGAN, M. D. L., CALVERLEY, P. M. A. & CLARK, C. J. 2001. Pulmonary rehabilitation. British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation. *Thorax*, 56, 827-34.
- MOXHAM, J. 1988. Aminophylline and the respiratory muscles: an alternative view. *Clin Chest Med*, 9, 325-36.
- MURCIANO, D., AUCLAIR, M. H., PARIENTE, R. & AUBIER, M. 1989. A randomized, controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. *N Engl J Med*, 320, 1521-5.
- MURPHY, T. F., SETHI, S., KLINGMAN, K. L., BRUEGGEMANN, A. B. & DOERN, G. V. 1999. Simultaneous respiratory tract colonization by multiple strains of nontypeable haemophilus influenzae in chronic obstructive pulmonary disease: implications for antibiotic therapy. *J Infect Dis*, 180, 404-9.
- NADEEM, N. J., TAYLOR, S. J. & ELDRIDGE, S. M. 2011. Withdrawal of inhaled corticosteroids in individuals with COPD--a systematic review and comment on trial methodology. *Respir Res*, 12, 107.
- NANNINI, L. J., LASSERSON, T. J. & POOLE, P. 2012. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 9, CD006829.
- NANNINI, L. J., POOLE, P., MILAN, S. J., HOLMES, R. & NORMANSELL, R. 2013a. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 11, CD003794.
- NANNINI, L. J., POOLE, P., MILAN, S. J. & KESTERTON, A. 2013b. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 8, CD006826.
- NATIONAL EMPHYSEMA TREATMENT TRIAL RESEARCH, G. 2001. Patients at High Risk of Death after Lung-Volume-Reduction Surgery. *N Engl J Med*, 345, 1075-1083.
- NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL 1998. A guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines. Canberra: NHMRC.
- NATIONAL HEART LUNG AND BLOOD INSTITUTE 1998. Morbidity and Mortality: Chartbook on Cardiovascular, Lung, and Blood Diseases [2004 edition available <http://www.nhlbi.nih.gov/resources/docs/cht-book.htm>]. Bethesda, MD: US Department of Health and Institutes of Health.
- NETT 1999. Rationale and design of the National Emphysema Treatment Trial (NETT): A prospective randomized trial of lung volume reduction surgery. *J Thorac Cardiovasc Surg*, 118, 518-28.
- NG, T. P., NITI, M., TAN, W. C., CAO, Z., ONG, K. C. & ENG, P. 2007. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. *Arch Intern Med*, 167, 60-7.
- NHLBI/WHO WORKSHOP REPORT April 2001. Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD): Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Bethesda, MD: National Institutes of Health - National Heart, Lung and Blood Institute.

- NHS CENTRE FOR REVIEWS AND DISSEMINATION 2003. Inhaler devices for the management of asthma and COPD. *Effective Healthcare: Bulletin on the Effectiveness of Health Service Interventions for Decision Makers*, 8, 1-12.
- NICHOL, K. L., MARGOLIS, K. L., WUORENMA, J. & VON STERNBERG, T. 1994. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med*, 331, 778-84.
- NITENBERG, A. & ANTONY, I. 1999. Effects of nicotine gum on coronary vasomotor responses during sympathetic stimulation in patients with coronary artery stenosis. *J Cardiovasc Pharmacol*, 34, 694-9.
- NOCTURNAL OXYGEN THERAPY TRIAL GROUP 1980. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med*, 93, 391-8.
- NONOYAMA, M. L., BROOKS, D., LACASSE, Y., GUYATT, G. H. & GOLDSTEIN, R. S. 2007. Oxygen therapy during exercise training in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD005372.
- O'DONNELL, D. E., REVILL, S. M. & WEBB, K. A. 2001. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 164, 770-7.
- O'DRISCOLL, B. R. 2008. Short burst oxygen therapy in patients with COPD. *Monaldi Arch Chest Dis*, 69, 70-4.
- O'NEILL, B., MAHON, J. M. & BRADLEY, J. 2006. Short-burst oxygen therapy in chronic obstructive pulmonary disease. *Respir Med*, 100, 1129-38.
- OGALE, S. S., LEE, T. A., AU, D. H., BOUDREAU, D. M. & SULLIVAN, S. D. 2010. Cardiovascular events associated with ipratropium bromide in COPD. *Chest*, 137, 13-9.
- OLENCHOCK, B. A., FONAROW, G. G., PAN, W., HERNANDEZ, A. & CANNON, C. P. 2009. Current use of beta blockers in patients with reactive airway disease who are hospitalized with acute coronary syndromes. *Am J Cardiol*, 103, 295-300.
- OMACHI, T. A., KATZ, P. P., YELIN, E. H., GREGORICH, S. E., IRIBARREN, C., BLANC, P. D. & EISNER, M. D. 2009. Depression and health-related quality of life in chronic obstructive pulmonary disease. *Am J Med*, 122, 778 e9-15.
- OMLAND, O., WURTZ, E. T., AASEN, T. B., BLANC, P., BRISMAN, J. B., MILLER, M. R., PEDERSEN, O. F., SCHLUNSEN, V., SIGSGAARD, T., ULRİK, C. S. & VISKUM, S. 2014. Occupational chronic obstructive pulmonary disease: a systematic literature review. *Scand J Work Environ Health*, 40, 19-35.
- ORA, J., LAVENEZIANA, P., OFIR, D., DEESOMCHOK, A., WEBB, K. A. & O'DONNELL, D. E. 2009. Combined effects of obesity and chronic obstructive pulmonary disease on dyspnea and exercise tolerance. *Am J Respir Crit Care Med*, 180, 964-71.
- ORENS, J. B., ESTENNE, M., ARCASOY, S., CONTE, J. V., CORRIS, P., EGAN, J. J., EGAN, T., KESHAVJEE, S., KNOOP, C., KOTLOFF, R., MARTINEZ, F. J., NATHAN, S., PALMER, S., PATTERSON, A., SINGER, L., SNELL, G., STUDER, S., VACHIERY, J. L. & GLANVILLE, A. R. 2006. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*, 25, 745-55.
- OSADNIK, C. R., MCDONALD, C. F., JONES, A. P. & HOLLAND, A. E. 2012. Airway clearance techniques for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 3, CD008328.
- OSADNIK, C. R., MCDONALD, C. F., MILLER, B. R., HILL, C. J., TARRANT, B., STEWARD, R., CHAO, C., STODDEN, N., OLIVEIRA, C. C., GAGLIARDI, N. & HOLLAND, A. E. 2014. The effect of positive expiratory pressure (PEP) therapy on symptoms, quality of life and incidence of re-exacerbation in patients with acute exacerbations of chronic obstructive pulmonary disease: a multicentre, randomised controlled trial. *Thorax*, 69, 137-43.
- OSBORNE, R. H., JORDAN, J. E. & ROGERS, A. 2008. A critical look at the role of self-management for people with arthritis and other chronic diseases. *Nat Clin Pract Rheumatol*, 4, 224-5.
- PARKES, G., GREENHALGH, T., GRIFFIN, M. & DENT, R. 2008. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomised controlled trial. *BMJ*, 336, 598-600.

- PATEL, A. R., DONALDSON, G. C., MACKAY, A. J., WEDZICHA, J. A. & HURST, J. R. 2012. The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. *Chest*, 141, 851-7.
- PATEL, I. S., SEEMUNGAL, T. A., WILKS, M., LLOYD-OWEN, S. J., DONALDSON, G. C. & WEDZICHA, J. A. 2002. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax*, 57, 759-64.
- PEACOCK, J. L., ANDERSON, H. R., BREMNER, S. A., MARSTON, L., SEEMUNGAL, T. A., STRACHAN, D. P. & WEDZICHA, J. A. 2011. Outdoor air pollution and respiratory health in patients with COPD. *Thorax*, 66, 591-6.
- PELLEGRINO, R., VIEGI, G., BRUSASCO, V., CRAPO, R. O., BURGOS, F., CASABURI, R., COATES, A., VAN DER GRINTEN, C. P., GUSTAFSSON, P., HANKINSON, J., JENSEN, R., JOHNSON, D. C., MACINTYRE, N., MCKAY, R., MILLER, M. R., NAVAJAS, D., PEDERSEN, O. F. & WANGER, J. 2005. Interpretative strategies for lung function tests. *Eur Respir J*, 26, 948-68.
- PEPIN, V., BRODEUR, J., LACASSE, Y., MILOT, J., LEBLANC, P., WHITTOM, F. & MALTAIS, F. 2007. Six-minute walking versus shuttle walking: responsiveness to bronchodilation in chronic obstructive pulmonary disease. *Thorax*, 62, 291-8.
- PEPIN, V., SAEY, D., WHITTOM, F., LEBLANC, P. & MALTAIS, F. 2005. Walking versus cycling: sensitivity to bronchodilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 172, 1517-22.
- PEPPER, J. K. & BREWER, N. T. 2014. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review. *Tob Control*, 23, 375-84.
- PETERS, M. J. & MORGAN, L. C. 2002. The pharmacotherapy of smoking cessation. *Med J Aust*, 176, 486-90.
- PETO, R., SPEIZER, F. E., COCHRANE, A. L., MOORE, F., FLETCHER, C. M., TINKER, C. M., HIGGINS, I. T., GRAY, R. G., RICHARDS, S. M., GILLILAND, J. & NORMAN-SMITH, B. 1983. The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. Results from 20 years of prospective observation. *Am Rev Respir Dis*, 128, 491-500.
- PEYTREMANN-BRIDEVAUX, I., STAEGER, P., BRIDEVAUX, P. O., GHALI, W. A. & BURNAND, B. 2008. Effectiveness of chronic obstructive pulmonary disease-management programs: systematic review and meta-analysis. *Am J Med*, 121, 433-443 e4.
- PHILLIPSON, E. A. & BOWES, G. 1986. Control of breathing during sleep. In: CHERNIACK, N. S. & WIDDICOMBE, J. G. (eds.) *Handbook of Physiology. The Respiratory System. Vol II. Control of Breathing*. Bethesda, MD: American Physiological Society.
- PINNOCK, H., HANLEY, J., MCCLOUGHAN, L., TODD, A., KRISHAN, A., LEWIS, S., STODDART, A., VAN DER POL, M., MACNEE, W., SHEIKH, A., PAGLIARI, C. & MCKINSTRY, B. 2013. Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial. *BMJ*, 347, f6070.
- PITTA, F., TROOSTERS, T., SPRUIT, M. A., PROBST, V. S., DECRAMER, M. & GOSSELINK, R. 2005. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 171, 972-7.
- PLANT, P. K., OWEN, J. L. & ELLIOTT, M. W. 2000. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet*, 355, 1931-5.
- POLLACK, M. H., KRADIN, R., OTTO, M. W., WORTHINGTON, J., GOULD, R., SABATINO, S. A. & ROSENBAUM, J. F. 1996. Prevalence of panic in patients referred for pulmonary function testing at a major medical center. *Am J Psychiatry*, 153, 110-3.
- POMERLEAU, C. S., POMERLEAU, O. F., NAMENEK, R. J. & MEHRINGER, A. M. 2000. Short-term weight gain in abstaining women smokers. *J Subst Abuse Treat*, 18, 339-42.
- POOLE, P. & BLACK, P. N. 2010. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD001287.
- POOLE, P. J., CHACKO, E., WOOD-BAKER, R. W. & CATES, C. J. 2006. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD002733.

- POSTMA, D. S., PETERS, I., STEENHUIS, E. J. & SLUITER, H. J. 1988. Moderately severe chronic airflow obstruction. Can corticosteroids slow down obstruction? *Eur Respir J*, 1, 22-6.
- POSTMA, D. S., STEENHUIS, E. J., VAN DER WEELE, L. T. & SLUITER, H. J. 1985. Severe chronic airflow obstruction: can corticosteroids slow down progression? *Eur J Respir Dis*, 67, 56-64.
- POULAIN, M., DOUCET, M., DRAPEAU, V., FOURNIER, G., TREMBLAY, A., POIRIER, P. & MALTAIS, F. 2008. Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary disease. *Chron Respir Dis*, 5, 35-41.
- POULAIN, M., DURAND, F., PALOMBA, B., CEUGNIET, F., DESPLAN, J., VARRAY, A. & PREFAUT, C. 2003. 6-minute walk testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD. *Chest*, 123, 1401-7.
- PROCHASKA, J. J. & HILTON, J. F. 2012. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. *BMJ*, 344, e2856.
- PUHAN, M., SCHARPLATZ, M., TROOSTERS, T., WALTERS, E. H. & STEURER, J. 2009a. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD005305.
- PUHAN, M. A., GARCIA-AYMERICH, J., FREY, M., TER RIET, G., ANTO, J. M., AGUSTI, A. G., GOMEZ, F. P., RODRIGUEZ-ROISIN, R., MOONS, K. G., KESSELS, A. G. & HELD, U. 2009c. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet*, 374, 704-11.
- PUHAN, M. A., GIMENO-SANTOS, E., SCHARPLATZ, M., TROOSTERS, T., WALTERS, E. H. & STEURER, J. 2011. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD005305.
- QUINT, J. K., HERRETT, E., BHASKARAN, K., TIMMIS, A., HEMINGWAY, H., WEDZICHA, J. A. & SMEETH, L. 2013. Effect of beta blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records. *BMJ*, 347, f6650.
- RABE, K. F., BATEMAN, E. D., O'DONNELL, D., WITTE, S., BREDENBROKER, D. & BETHKE, T. D. 2005. Roflumilast--an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*, 366, 563-71.
- RAM, F. S., JONES, P. W., CASTRO, A. A., DE BRITO, J. A., ATALLAH, A. N., LACASSE, Y., MAZZINI, R., GOLDSTEIN, R. & CENDON, S. 2002. Oral theophylline for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD003902.
- RAM, F. S., PICOT, J., LIGHTOWLER, J. & WEDZICHA, J. A. 2004. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD004104.
- RAM, F. S. & SESTINI, P. 2003. Regular inhaled short acting beta2 agonists for the management of stable chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *Thorax*, 58, 580-4.
- RAM, F. S. & WEDZICHA, J. A. 2002. Ambulatory oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD000238.
- RAMACHANDRAN, K., MCCUSKER, C., CONNORS, M., ZUWALLACK, R. & LAHIRI, B. 2008. The influence of obesity on pulmonary rehabilitation outcomes in patients with COPD. *Chron Respir Dis*, 5, 205-9.
- REA, H., KENEALY, T., ADAIR, J., ROBINSON, E. & SHERIDAN, N. 2011. Spirometry for patients in hospital and one month after admission with an acute exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis*, 6, 527-32.
- REA, H., MCAULEY, S., JAYARAM, L., GARRETT, J., HOCKEY, H., STOREY, L., O'DONNELL, G., HARU, L., PAYTON, M. & O'DONNELL, K. 2010. The clinical utility of long-term humidification therapy in chronic airway disease. *Respir Med*, 104, 525-33.
- RENNARD, S. I., SCHACHTER, N., STREK, M., RICKARD, K. & AMIT, O. 2006. Cilomilast for COPD: results of a 6-month, placebo-controlled study of a potent, selective inhibitor of phosphodiesterase 4. *Chest*, 129, 56-66.
- REVILL, S. M., WILLIAMS, J., SEWELL, L., COLLIER, R. & SINGH, S. J. 2009. Within-day repeatability of the endurance shuttle walk test. *Physiotherapy*, 95, 140-3.

- RICE, K. L., DEWAN, N., BLOOMFIELD, H. E., GRILL, J., SCHULT, T. M., NELSON, D. B., KUMARI, S., THOMAS, M., GEIST, L. J., BEANER, C., CALDWELL, M. & NIEWOEHNER, D. E. 2010. Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med*, 182, 890-6.
- RICE, V. H., HARTMANN-BOYCE, J. & STEAD, L. F. 2013. Nursing interventions for smoking cessation. *Cochrane Database Syst Rev*, 8, CD001188.
- RICE, V. H. & STEAD, L. F. 2004. Nursing interventions for smoking cessation. *Cochrane Database Syst Rev*, CD001188.
- RIES, A. L., BAULDOFF, G. S., CARLIN, B. W., CASABURI, R., EMERY, C. F., MAHLER, D. A., MAKE, B., ROCHESTER, C. L., ZUWALLACK, R. & HERRERIAS, C. 2007. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest*, 131, 4S-42S.
- RIES, A. L., KAPLAN, R. M., LIMBERG, T. M. & PREWITT, L. M. 1995. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med*, 122, 823-32.
- RIES, A. L., MAKE, B. J., LEE, S. M., KRASNA, M. J., BARTELS, M., CROUCH, R. & FISHMAN, A. P. 2005. The effects of pulmonary rehabilitation in the national emphysema treatment trial. *Chest*, 128, 3799-809.
- RIETEMA, H., HOLVERDA, S., BOGAARD, H. J., MARCUS, J. T., SMIT, H. J., WESTERHOF, N., POSTMUS, P. E., BOONSTRA, A. & VONK-NOORDEGRAAF, A. 2008. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. *Eur Respir J*, 31, 759-64.
- RIVERA-FERNANDEZ, R., NAVARRETE-NAVARRO, P., FERNANDEZ-MONDEJAR, E., RODRIGUEZ-ELVIRA, M., GUERRERO-LOPEZ, F. & VAZQUEZ-MATA, G. 2006. Six-year mortality and quality of life in critically ill patients with chronic obstructive pulmonary disease. *Crit Care Med*, 34, 2317-24.
- RIZKALLAH, J., MAN, S. F. & SIN, D. D. 2009. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. *Chest*, 135, 786-93.
- RODRIGO, G. J., CASTRO-RODRIGUEZ, J. A. & PLAZA, V. 2009. Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting beta-agonists monotherapy for stable COPD: a systematic review. *Chest*, 136, 1029-38.
- RODRIGO, G. J. & PLAZA, V. 2014. Efficacy and safety of a fixed-dose combination of indacaterol and Glycopyrronium for the treatment of COPD: a systematic review. *Chest*, 146, 309-17.
- RODRIGUEZ, E., FERRER, J., MARTI, S., ZOCK, J. P., PLANA, E. & MORELL, F. 2008. Impact of occupational exposure on severity of COPD. *Chest*, 134, 1237-43.
- ROEDE, B. M., BRESSER, P., BINDELS, P. J., KOK, A., PRINS, M., TER RIET, G., GESKUS, R. B., HERINGS, R. M. & PRINS, J. M. 2008. Antibiotic treatment is associated with reduced risk of a subsequent exacerbation in obstructive lung disease: an historical population based cohort study. *Thorax*, 63, 968-73.
- ROEHRS, T., MERRION, M., PEDROSI, B., STEPANSKI, E., ZORICK, F. & ROTH, T. 1995. Neuropsychological function in obstructive sleep apnea syndrome (OSAS) compared to chronic obstructive pulmonary disease (COPD). *Sleep*, 18, 382-8.
- ROSSI, A., GOTTFRIED, S. B., HIGGS, B. D., ZOCCHI, L., GRASSINO, A. & MILIC-EMILI, J. 1985. Respiratory mechanics in mechanically ventilated patients with respiratory failure. *J Appl Physiol*, 58, 1849-58.
- RUTTEN, E. P., FRANSEN, F. M., SPRUIT, M. A. & WOUTERS, E. F. 2013. Anemia is associated with bone mineral density in chronic obstructive pulmonary disease. *COPD*, 10, 286-92.
- RUTTEN, F. H., ZUITHOFF, N. P., HAK, E., GROBBEE, D. E. & HOES, A. W. 2010. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. *Arch Intern Med*, 170, 880-7.
- SABIT, R., GRIFFITHS, T. L., WATKINS, A. J., EVANS, W., BOLTON, C. E., SHALE, D. J. & LEWIS, K. E. 2008. Predictors of poor attendance at an outpatient pulmonary rehabilitation programme. *Respir Med*, 102, 819-24.
- SAJKOV, D., MCEVOY, R. D., COWIE, R. J., BRADLEY, J. A., ANTIC, R., MORRIS, R. G. & FRITH, P. A. 1993. Felodipine improves pulmonary hemodynamics in chronic obstructive pulmonary disease. *Chest*, 103, 1354-61.

- SAJKOV, D., WANG, T., FRITH, P. A., BUNE, A. J., ALPERS, J. A. & MCEVOY, R. D. 1997. A comparison of two long-acting vasoselective calcium antagonists in pulmonary hypertension secondary to COPD. *Chest*, 111, 1622-30.
- SAKAE, T. M., PIZZICHINI, M. M., TEIXEIRA, P. J., SILVA, R. M., TREVISOL, D. J. & PIZZICHINI, E. 2013. Exacerbations of COPD and symptoms of gastroesophageal reflux: a systematic review and meta-analysis. *J Bras Pneumol*, 39, 259-71.
- SALPETER, S., ORMISTON, T. & SALPETER, E. 2002. Cardioselective beta-blockers for reversible airway disease. *Cochrane Database Syst Rev*, CD002992.
- SALPETER, S., ORMISTON, T. & SALPETER, E. 2005. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD003566.
- SALPETER, S. R., BUCKLEY, N. S. & SALPETER, E. E. 2006. Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. *J Gen Intern Med*, 21, 1011-9.
- SAMBROOK, P. N., SEEMAN, E., PHILLIPS, S. R. & EBELING, P. R. 2002. Preventing osteoporosis: outcomes of the Australian Fracture Prevention Summit. *Med J Aust*, 176 Suppl, S1-16.
- SANTO TOMAS, L. H. 2011. Emphysema and chronic obstructive pulmonary disease in coal miners. *Curr Opin Pulm Med*, 17, 123-5.
- SASAKI, T., NAKAYAMA, K., YASUDA, H., YOSHIDA, M., ASAMURA, T., OHROI, T., ARAI, H., ARAYA, J., KUWANO, K. & YAMAYA, M. 2009. A randomized, single-blind study of lansoprazole for the prevention of exacerbations of chronic obstructive pulmonary disease in older patients. *J Am Geriatr Soc*, 57, 1453-7.
- SCHANE, R. E., WALTER, L. C., DINNO, A., COVINSKY, K. E. & WOODRUFF, P. G. 2008. Prevalence and risk factors for depressive symptoms in persons with chronic obstructive pulmonary disease. *J Gen Intern Med*, 23, 1757-62.
- SCHARF, S. M., IQBAL, M., KELLER, C., CRINER, G., LEE, S. & FESSLER, H. E. 2002. Hemodynamic characterization of patients with severe emphysema. *Am J Respir Crit Care Med*, 166, 314-22.
- SCHNELL, K., WEISS, C. O., LEE, T., KRISHNAN, J. A., LEFF, B., WOLFF, J. L. & BOYD, C. 2012. The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 1999-2008. *BMC Pulm Med*, 12, 26.
- SCHOLS, A. M., BROEKHUIZEN, R., WELING-SCHEEPERS, C. A. & WOUTERS, E. F. 2005. Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr*, 82, 53-9.
- SCHONHOFER, B., WENZEL, M., GEIBEL, M. & KOHLER, D. 1998. Blood transfusion and lung function in chronically anemic patients with severe chronic obstructive pulmonary disease. *Crit Care Med*, 26, 1824-8.
- SCHOU, L., OSTERGAARD, B., RASMUSSEN, L. S., RYDAHL-HANSEN, S. & PHANARETH, K. 2012. Cognitive dysfunction in patients with chronic obstructive pulmonary disease--a systematic review. *Respir Med*, 106, 1071-81.
- SCHWARTZ, J. L. 1987. Review and Evaluation of Smoking Cessation Methods: The United States and Canada, 1978-1985 (NIH Publication No.87-2940). Bethesda, MD.: National Cancer Institute, National Institutes of Health.
- SCIURBA, F. C., ERNST, A., HERTH, F. J., STRANGE, C., CRINER, G. J., MARQUETTE, C. H., KOVITZ, K. L., CHIACCHIERINI, R. P., GOLDIN, J. & MCLENNAN, G. 2010. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med*, 363, 1233-44.
- SEEMUNGAL, T., HARPER-OWEN, R., BHOWMIK, A., MORIC, I., SANDERSON, G., MESSAGE, S., MACCALLUM, P., MEADE, T. W., JEFFRIES, D. J., JOHNSTON, S. L. & WEDZICHA, J. A. 2001. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 164, 1618-23.
- SEEMUNGAL, T. A., WILKINSON, T. M., HURST, J. R., PERERA, W. R., SAPSFORD, R. J. & WEDZICHA, J. A. 2008. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med*, 178, 1139-47.
- SELROOS, O., BORGSTROM, L. & INGELF, J. 2009. Use of dry powder inhalers in acute exacerbations of asthma and COPD. *Ther Adv Respir Dis*, 3, 81-91.

- SENDEROVITZ, T., VESTBO, J., FRANDSEN, J., MALTBAEK, N., NORGAARD, M., NIELSEN, C. & KAMPMANN, J. P. 1999. Steroid reversibility test followed by inhaled budesonide or placebo in outpatients with stable chronic obstructive pulmonary disease. The Danish Society of Respiratory Medicine. *Respir Med*, 93, 715-8.
- SERGINSON, J. G., YANG, I. A., ARMSTRONG, J. G., COOPER, D. M., MATTHIESSEN, A. M., MORRISON, S. C., GAIR, J. M., COOPER, B. & ZIMMERMAN, P. V. 2009. Variability in the rate of prescription and cost of domiciliary oxygen therapy in Australia. *Med J Aust*, 191, 549-53.
- SHAH, P. L. & HERTH, F. J. 2014. Current status of bronchoscopic lung volume reduction with endobronchial valves. *Thorax*, 69, 280-6.
- SHANMUGAM, G., BHUTANI, S., KHAN, D. A. & BROWN, E. S. 2007. Psychiatric considerations in pulmonary disease. *Psychiatr Clin North Am*, 30, 761-80.
- SHARAFKHANEH, A., SOUTHARD, J. G., GOLDMAN, M., URYNIAK, T. & MARTIN, U. J. 2013. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. *Respir Med*, 106, 257-68.
- SHEPPERD, S., HARWOOD, D., JENKINSON, C., GRAY, A., VESSEY, M. & MORGAN, P. 1998. Randomised controlled trial comparing hospital at home care with inpatient hospital care. I: three month follow up of health outcomes. *BMJ*, 316, 1786-91.
- SHIFFMAN, S. 2005. Nicotine lozenge efficacy in light smokers. *Drug Alcohol Depend*, 77, 311-4.
- SHIFFMAN, S. & FERGUSON, S. G. 2008. Nicotine patch therapy prior to quitting smoking: a meta-analysis. *Addiction*, 103, 557-63.
- SHIRTCLIFFE, P., MARSH, S., TRAVERS, J., WEATHERALL, M. & BEASLEY, R. 2012. Childhood asthma and GOLD-defined chronic obstructive pulmonary disease. *Intern Med J*, 42, 83-88.
- SHIRTCLIFFE, P., WEATHERALL, M., MARSH, S., TRAVERS, J., HANSELL, A., MCNAUGHTON, A., ALDINGTON, S., MUELLEROVA, H. & BEASLEY, R. 2007. COPD prevalence in a random population survey: a matter of definition. *European Respiratory Journal*, 30, 232-239.
- SHORR, A. F., DOYLE, J., STERN, L., DOLGITSER, M. & ZILBERBERG, M. D. 2008. Anemia in chronic obstructive pulmonary disease: epidemiology and economic implications. *Curr Med Res Opin*, 24, 1123-30.
- SHORR, A. F., SUN, X., JOHANNES, R. S., YAITANES, A. & TABAK, Y. P. 2011. Validation of a novel risk score for severity of illness in acute exacerbations of COPD. *Chest*, 140, 1177-83.
- SHORT, P. M., LIPWORTH, S. I., ELDER, D. H., SCHEMBRI, S. & LIPWORTH, B. J. 2011. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. *BMJ*, 342, d2549.
- SIAFAKAS NM & BOUROS D 1998. Management of acute exacerbation of chronic obstructive pulmonary disease. In: POSTMA, D. & SIAFAKAS NM (eds.) *Management of Chronic Obstructive Pulmonary Disease*. Sheffield: ERS Monograph.
- SIAFAKAS, N. M., VERMEIRE, P., PRIDE, N. B., PAOLETTI, P., GIBSON, J., HOWARD, P., YERNAULT, J. C., DECRAMER, M., HIGENBOTTAM, T., POSTMA, D. S. & ET AL. 1995. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J*, 8, 1398-420.
- SIMBERKOFF, M. S., CROSS, A. P., AL-IBRAHIM, M., BALCH, A. L., GEISELER, P. J., NADLER, J., RICHMOND, A. S., SMITH, R. P., SCHIFFMAN, G., SHEPARD, D. S. & ET AL. 1986. Efficacy of pneumococcal vaccine in high-risk patients. Results of a Veterans Administration Cooperative Study. *N Engl J Med*, 315, 1318-27.
- SIMONNEAU, G., ROBBINS, I. M., BEGHETTI, M., CHANNICK, R. N., DELCROIX, M., DENTON, C. P., ELLIOTT, C. G., GAINE, S. P., GLADWIN, M. T., JING, Z. C., KROWKA, M. J., LANGLEBEN, D., NAKANISHI, N. & SOUZA, R. 2009. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*, 54, S43-54.
- SIN, D. D., BELL, N. R., SVENSON, L. W. & MAN, S. F. 2002. The impact of follow-up physician visits on emergency readmissions for patients with asthma and chronic obstructive pulmonary disease: a population-based study. *Am J Med*, 112, 120-5.
- SINCLAIR, H. K., BOND, C. M. & STEAD, L. F. 2004. Community pharmacy personnel interventions for smoking cessation. *Cochrane Database Syst Rev*, CD003698.

- SINGH, B., MIELKE, M. M., PARSAIK, A. K., CHA, R. H., ROBERTS, R. O., SCANLON, P. D., GEDA, Y. E., CHRISTIANSON, T. J., PANKRATZ, V. S. & PETERSEN, R. C. 2014. A prospective study of chronic obstructive pulmonary disease and the risk for mild cognitive impairment. *JAMA Neurol*, 71, 581-8.
- SINGH, S., LOKE, Y. K., ENRIGHT, P. & FURBERG, C. D. 2013. Pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergic medications. *Thorax*, 68, 114-6.
- SINGH, S., LOKE, Y. K. & FURBERG, C. D. 2008. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Jama*, 300, 1439-50.
- SINGH, S., LOKE, Y. K., SPANGLER, J. G. & FURBERG, C. D. 2011. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *CMAJ*, 183, 1359-66.
- SKWARSKA, E., COHEN, G., SKWARSKI, K. M., LAMB, C., BUSHELL, D., PARKER, S. & MACNEE, W. 2000. Randomized controlled trial of supported discharge in patients with exacerbations of chronic obstructive pulmonary disease. *Thorax*, 55, 907-12.
- SLATORE, C. G., BRYSON, C. L. & AU, D. H. 2009. The association of inhaled corticosteroid use with serum glucose concentration in a large cohort. *Am J Med*, 122, 472-8.
- SMITH, B. M., PRINCE, M. R., HOFFMAN, E. A., BLUEMKE, D. A., LIU, C. Y., RABINOWITZ, D., HUEPER, K., PARIKH, M. A., GOMES, A. S., MICHOS, E. D., LIMA, J. A. & BARR, R. G. 2013. Impaired left ventricular filling in COPD and emphysema: is it the heart or the lungs? The Multi-Ethnic Study of Atherosclerosis COPD Study. *Chest*, 144, 1143-51.
- SMITH, C. B., KANNER, R. E., GOLDEN, C. A., KLAUBER, M. R. & RENZETTI, A. D., JR. 1980. Effect of viral infections on pulmonary function in patients with chronic obstructive pulmonary diseases. *J Infect Dis*, 141, 271-80.
- SMOLLER, J. W., POLLACK, M. H., OTTO, M. W., ROSENBAUM, J. F. & KRADIN, R. L. 1996. Panic anxiety, dyspnea, and respiratory disease. Theoretical and clinical considerations. *Am J Respir Crit Care Med*, 154, 6-17.
- SOLER, N., TORRES, A., EWIG, S., GONZALEZ, J., CELIS, R., EL-EBIARY, M., HERNANDEZ, C. & RODRIGUEZ-ROISIN, R. 1998. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med*, 157, 1498-505.
- SOURK, R. L. & NUGENT, K. M. 1983. Bronchodilator testing: confidence intervals derived from placebo inhalations. *Am Rev Respir Dis*, 128, 153-7.
- SPENCER, S., KARNER, C., CATES, C. J. & EVANS, D. J. 2011. Inhaled corticosteroids versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD007033.
- SPRENKLE, M. D., NIEWOEHNER, D. E., MACDONALD, R., RUTKS, I. & WILT, T. J. 2004. Clinical Efficacy of OM-85 BV in COPD and Chronic Bronchitis: A Systematic Review. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, 2, 167 - 175.
- SPRUIT, M. A., SINGH, S. J., GARVEY, C., ZUWALLACK, R., NICI, L., ROCHESTER, C., HILL, K., HOLLAND, A. E., LAREAU, S. C., MAN, W. D., PITTA, F., SEWELL, L., RASKIN, J., BOURBEAU, J., CROUCH, R., FRANSSEN, F. M., CASABURI, R., VERCOULEN, J. H., VOGIATZIS, I., GOSSELINK, R., CLINI, E. M., EFFING, T. W., MALTAIS, F., VAN DER PALEN, J., TROOSTERS, T., JANSSEN, D. J., COLLINS, E., GARCIA-AYMERICH, J., BROOKS, D., FAHY, B. F., PUHAN, M. A., HOOGENDOORN, M., GARROD, R., SCHOLS, A. M., CARLIN, B., BENZO, R., MEEK, P., MORGAN, M., RUTTEN-VAN MOLKEN, M. P., RIES, A. L., MAKE, B., GOLDSTEIN, R. S., DOWSON, C. A., BROZEK, J. L., DONNER, C. F. & WOUTERS, E. F. 2013. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*, 188, e13-64.
- SRIDHAR MK, L. M. 2006. Nutritional consequences of disease. *Medicine*, 34, 530-532.
- STAPLETON, R. D., NIELSEN, E. L., ENGELBERG, R. A., PATRICK, D. L. & CURTIS, J. R. 2005. Association of depression and life-sustaining treatment preferences in patients with COPD. *Chest*, 127, 328-34.
- STEAD, L. F., BUITRAGO, D., PRECIADO, N., SANCHEZ, G., HARTMANN-BOYCE, J. & LANCASTER, T. 2013a. Physician advice for smoking cessation. *Cochrane Database Syst Rev*, 5, CD000165.

- STEAD, L. F., HARTMANN-BOYCE, J., PERERA, R. & LANCASTER, T. 2013c. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev*, 8, CD002850.
- STEAD, L. F. & LANCASTER, T. 2005. Group behaviour therapy programmes for smoking cessation. *Cochrane Database Syst Rev*, CD001007.
- STEAD, L. F., PERERA, R., BULLEN, C., MANT, D., HARTMANN-BOYCE, J., CAHILL, K. & LANCASTER, T. 2012. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*, 11, CD000146.
- STEAD, L. F., PERERA, R., BULLEN, C., MANT, D. & LANCASTER, T. 2008. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*, CD000146.
- STEER, J., NORMAN, E. M., AFOLABI, O. A., GIBSON, G. J. & BOURKE, S. C. 2012. Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. *Thorax*, 67, 117-21.
- STEPHENSON, A., SEITZ, D., BELL, C. M., GRUNEIR, A., GERSHON, A. S., AUSTIN, P. C., FU, L., ANDERSON, G. M., ROCHON, P. A. & GILL, S. S. 2011. Inhaled anticholinergic drug therapy and the risk of acute urinary retention in chronic obstructive pulmonary disease: a population-based study. *Arch Intern Med*, 171, 914-20.
- STOCKLEY, R. A., O'BRIEN, C., PYE, A. & HILL, S. L. 2000. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest*, 117, 1638-45.
- STOLZ, D., RASCH, H., LINKA, A., DI VALENTINO, M., MEYER, A., BRUTSCHE, M. & TAMM, M. 2008. A randomised, controlled trial of bosentan in severe COPD. *Eur Respir J*, 32, 619-28.
- STRASSMANN, R., BAUSCH, B., SPAAR, A., KLEIJNEN, J., BRAENDLI, O. & PUHAN, M. A. 2009. Smoking cessation interventions in COPD: a network meta-analysis of randomised trials. *Eur Respir J*, 34, 634-40.
- STRUIK, F. M., LACASSE, Y., GOLDSTEIN, R., KERSTJENS, H. M. & WIJKSTRA, P. J. 2013. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 6, CD002878.
- STRUIK, F. M., LACASSE, Y., GOLDSTEIN, R. S., KERSTJENS, H. A. & WIJKSTRA, P. J. 2014. Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. *Respir Med*, 108, 329-37.
- SUGAWARA, K., TAKAHASHI, H., KASAI, C., KIYOKAWA, N., WATANABE, T., FUJII, S., KASHIWAGURA, T., HONMA, M., SATAKE, M. & SHIOYA, T. 2010. Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. *Respir Med*, 104, 1883-9.
- SUZUKI, M., MURO, S., ANDO, Y., OMORI, T., SHIOTA, T., ENDO, K., SATO, S., AIHARA, K., MATSUMOTO, M., SUZUKI, S., ITOTANI, R., ISHITOKO, M., HARA, Y., TAKEMURA, M., UEDA, T., KAGIOKA, H., HIRABAYASHI, M., FUKUI, M. & MISHIMA, M. 2012. A randomized, placebo-controlled trial of acupuncture in patients with chronic obstructive pulmonary disease (COPD): the COPD-acupuncture trial (CAT). *Arch Intern Med*, 172, 878-86.
- TABAK, Y. P., SUN, X., JOHANNES, R. S., GUPTA, V. & SHORR, A. F. 2009. Mortality and need for mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease: development and validation of a simple risk score. *Arch Intern Med*, 169, 1595-602.
- TAN, W. C., VOLLMER, W. M., LAMPRECHT, B., MANNINO, D. M., JITHOO, A., NIZANKOWSKA-MOGILNICKA, E., MEJZA, F., GISLASON, T., BURNEY, P. G. & BUIST, A. S. 2012. Worldwide patterns of bronchodilator responsiveness: results from the Burden of Obstructive Lung Disease study. *Thorax*, 67, 718-26.
- TANDON, M. K., PHILLIPS, M., WATERER, G., DUNKLEY, M., COMANS, P. & CLANCY, R. 2010. Oral immunotherapy with inactivated nontypeable *Haemophilus influenzae* reduces severity of acute exacerbations in severe COPD. *Chest*, 137, 805-11.
- TANG, C. Y., TAYLOR, N. F. & BLACKSTOCK, F. C. 2010. Chest physiotherapy for patients admitted to hospital with an acute exacerbation of chronic obstructive pulmonary disease (COPD): a systematic review. *Physiotherapy*, 96, 1-13.
- TARPY, S. P. & CELLI, B. R. 1995. Long-term oxygen therapy. *N Engl J Med*, 333, 710-4.
- TASHKIN, D. P., ALTOSE, M. D., CONNETT, J. E., KANNER, R. E., LEE, W. W. & WISE, R. A. 1996. Methacholine reactivity predicts changes in lung function over time in smokers with early

- chronic obstructive pulmonary disease. The Lung Health Study Research Group. *Am J Respir Crit Care Med*, 153, 1802-11.
- TASHKIN, D. P., CELLI, B., SENN, S., BURKHART, D., KESTEN, S., MENJOGE, S. & DECRAMER, M. 2008. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*, 359, 1543-54.
- TASHKIN, D. P., LI, N., HALPIN, D., KLEERUP, E., DECRAMER, M., CELLI, B. & ELASHOFF, R. 2013. Annual rates of change in pre- vs. post-bronchodilator FEV1 and FVC over 4 years in moderate to very severe COPD. *Respir Med*, 107, 1904-11.
- TASHKIN, D. P., RENNARD, S., HAYS, J. T., MA, W., LAWRENCE, D. & LEE, T. C. 2011a. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. *Chest*, 139, 591-9.
- TASHKIN, D. P., RENNARD, S., TAYLOR HAYS, J., LAWRENCE, D., MARTON, J. P. & LEE, T. C. 2011b. Lung function and respiratory symptoms in a 1-year randomized smoking cessation trial of varenicline in COPD patients. *Respir Med*, 105, 1682-90.
- TAYLOR, D. R., BUICK, B., KINNEY, C., LOWRY, R. C. & MCDEVITT, D. G. 1985. The efficacy of orally administered theophylline, inhaled salbutamol, and a combination of the two as chronic therapy in the management of chronic bronchitis with reversible air-flow obstruction. *Am Rev Respir Dis*, 131, 747-51.
- TERADA, K., MURO, S., OHARA, T., KUDO, M., OGAWA, E., HOSHINO, Y., HIRAI, T., NIIMI, A., CHIN, K. & MISHIMA, M. 2010. Abnormal swallowing reflex and COPD exacerbations. *Chest*, 137, 326-32.
- TERADA, K., MURO, S., SATO, S., OHARA, T., HARUNA, A., MARUMO, S., KINOSE, D., OGAWA, E., HOSHINO, Y., NIIMI, A., TERADA, T. & MISHIMA, M. 2008. Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation. *Thorax*, 63, 951-5.
- THAON, I., THIEBAUT, A., JOCHAULT, L., LEFEBVRE, A., LAPLANTE, J. J. & DALPHIN, J. C. 2011. Influence of hay and animal feed exposure on respiratory status: a longitudinal study. *Eur Respir J*, 37, 767-74.
- THOMPSON, A. B., MUELLER, M. B., HEIRES, A. J., BOHLING, T. L., DAUGHTON, D., YANCEY, S. W., SYKES, R. S. & RENNARD, S. I. 1992. Aerosolized beclomethasone in chronic bronchitis. Improved pulmonary function and diminished airway inflammation. *Am Rev Respir Dis*, 146, 389-95.
- TOELLE, B. G., XUAN, W., BIRD, T. E., ABRAMSON, M. J., ATKINSON, D. N., BURTON, D. L., JAMES, A. L., JENKINS, C. R., JOHNS, D. P., MAGUIRE, G. P., MUSK, A. W., WALTERS, E. H., WOOD-BAKER, R., HUNTER, M. L., GRAHAM, B. J., SOUTHWELL, P. J., VOLLMER, W. M., BUIST, A. S. & MARKS, G. B. 2013. Respiratory symptoms and illness in older Australians: the Burden of Obstructive Lung Disease (BOLD) study. *Med J Aust*, 198, 144-8.
- TONNESEN, P., CARROZZI, L., FAGERSTROM, K. O., GRATZIOU, C., JIMENEZ-RUIZ, C., NARDINI, S., VIEGI, G., LAZZARO, C., CAMPELL, I. A., DAGLI, E. & WEST, R. 2007. Smoking cessation in patients with respiratory diseases: a high priority, integral component of therapy. *Eur Respir J*, 29, 390-417.
- TONNESEN, P., MIKKELSEN, K. & BREMANN, L. 2006. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. *Chest*, 130, 334-42.
- TRAPPENBURG, J. C., MONNINKHOF, E. M., BOURBEAU, J., TROOSTERS, T., SCHRIJVERS, A. J., VERHEIJ, T. J. & LAMMERS, J. W. 2011. Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial. *Thorax*, 66, 977-84.
- TRIVEDI, R., RICHARD, N., MEHTA, R. & CHURCH, A. 2014. Umeclidinium in patients with COPD: a randomised, placebo-controlled study. *Eur Respir J*, 43, 72-81.
- TROOSTERS, T., CASABURI, R., GOSSELINK, R. & DECRAMER, M. 2005. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 172, 19-38.
- TSE, H. N., RAITERI, L., WONG, K. Y., YEE, K. S., NG, L. Y., WAI, K. Y., LOO, C. K. & CHAN, M. H. 2013. High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. *Chest*, 144, 106-18.

- TURNER, S. E., EASTWOOD, P. R., CECINS, N. M., HILLMAN, D. R. & JENKINS, S. C. 2004. Physiologic responses to incremental and self-paced exercise in COPD: a comparison of three tests. *Chest*, 126, 766-73.
- UCHIDA, H., SUZUKI, T., MAMO, D. C., MULSANT, B. H., KIKUCHI, T., TAKEUCHI, H., TOMITA, M., WATANABE, K., YAGI, G. & KASHIMA, H. 2009. Benzodiazepine and antidepressant use in elderly patients with anxiety disorders: a survey of 796 outpatients in Japan. *J Anxiety Disord*, 23, 477-81.
- ULRIK, C. S. 2014. Clinical benefit of fixed-dose dual bronchodilation with glycopyrronium and indacaterol once daily in patients with chronic obstructive pulmonary disease: a systematic review. *Int J Chron Obstruct Pulmon Dis*, 9, 331-8.
- US PUBLIC HEALTH SERVICE 2000. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. *JAMA*, 283, 3244-54.
- VAN BOVEN, J. F., CHAVANNES, N. H., VAN DER MOLEN, T., RUTTEN-VAN MOLKEN, M. P., POSTMA, M. J. & VEGTER, S. 2014. Clinical and economic impact of non-adherence in COPD: a systematic review. *Respir Med*, 108, 103-13.
- VAN DER MEER, R. M., WAGENA, E. J., OSTELO, R. W., JACOBS, J. E. & VAN SCHAYCK, C. P. 2003. Smoking cessation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD002999.
- VAN DER PALEN, J., GINKO, T., KROKER, A., VAN DER VALK, P., GOOSENS, M., PADULLES, L., SEOANE, B., REKEDA, L. & GARCIA GIL, E. 2013. Preference, satisfaction and errors with two dry powder inhalers in patients with COPD. *Expert Opin Drug Deliv*, 10, 1023-31.
- VAN GESTEL, Y. R., HOEKS, S. E., SIN, D. D., STAM, H., MERTENS, F. W., BAX, J. J., VAN DOMBURG, R. T. & POLDERMANS, D. 2009. Beta-blockers and health-related quality of life in patients with peripheral arterial disease and COPD. *Int J Chron Obstruct Pulmon Dis*, 4, 177-83.
- VAN GESTEL, Y. R., HOEKS, S. E., SIN, D. D., WELTEN, G. M., SCHOUTEN, O., WITTEVEEN, H. J., SIMSEK, C., STAM, H., MERTENS, F. W., BAX, J. J., VAN DOMBURG, R. T. & POLDERMANS, D. 2008. Impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. *Am J Respir Crit Care Med*, 178, 695-700.
- VANFLETEREN, L. E., FRANSSEN, F. M., USZKO-LENCER, N. H., SPRUIT, M. A., CELIS, M., GORGELS, A. P. & WOUTERS, E. F. 2011. Frequency and relevance of ischemic electrocardiographic findings in patients with chronic obstructive pulmonary disease. *Am J Cardiol*, 108, 1669-74.
- VATHENEN, A. S., BRITTON, J. R., EBDEN, P., COOKSON, J. B., WHARRAD, H. J. & TATTERSFIELD, A. E. 1988. High-dose inhaled albuterol in severe chronic airflow limitation. *Am Rev Respir Dis*, 138, 850-5.
- VESTBO, J., ANDERSON, J. A., CALVERLEY, P. M., CELLI, B., FERGUSON, G. T., JENKINS, C., KNOBIL, K., WILLITS, L. R., YATES, J. C. & JONES, P. W. 2009. Adherence to inhaled therapy, mortality and hospital admission in COPD. *Thorax*, 64, 939-43.
- VESTBO, J., PRESCOTT, E., ALMDAL, T., DAHL, M., NORDESTGAARD, B. G., ANDERSEN, T., SORENSEN, T. I. & LANGE, P. 2006. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med*, 173, 79-83.
- VESTBO, J., SORENSEN, T., LANGE, P., BRIX, A., TORRE, P. & VISKUM, K. 1999. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*, 353, 1819-23.
- VIVODTZEV, I., TAMISIER, R., BAGUET, J. P., BOREL, J. C., LEVY, P. & PEPIN, J. L. 2014. Arterial stiffness in COPD. *Chest*, 145, 861-75.
- VOGELMEIER, C., HEDERER, B., GLAAB, T., SCHMIDT, H., RUTTEN-VAN MOLKEN, M. P., BEEH, K. M., RABE, K. F. & FABBRI, L. M. 2011. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med*, 364, 1093-1103.
- VOGELMEIER, C. F., BATEMAN, E. D., PALLANTE, J., ALAGAPPAN, V. K., D'ANDREA, P., CHEN, H. & BANERJI, D. 2013. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease

- (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir Med*, 1, 51-60.
- VOLLENWEIDER, D. J., JARRETT, H., STEURER-STEY, C. A., GARCIA-AYMERICH, J. & PUHAN, M. A. 2012. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 12, CD010257.
- VONBANK, K., ZIESCHE, R., HIGENBOTTAM, T. W., STIEBELLEHNER, L., PETKOV, V., SCHENK, P., GERMANN, P. & BLOCK, L. H. 2003. Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. *Thorax*, 58, 289-93.
- VOZORIS, N. T., FISCHER, H. D., WANG, X., STEPHENSON, A. L., GERSHON, A. S., GRUNEIR, A., AUSTIN, P. C., ANDERSON, G. M., BELL, C. M., GILL, S. S. & ROCHON, P. A. 2014. Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J*, 44, 332-40.
- WAGNER, E. H., AUSTIN, B. T. & VON KORFF, M. 1996. Organizing care for patients with chronic illness. *Milbank Q*, 74, 511-44.
- WAKABAYASHI, K., GONZALEZ, M. A., DELHAYE, C., BEN-DOR, I., MALUENDA, G., COLLINS, S. D., SYED, A. I., GAGLIA, M. A., JR., TORGUSON, R., XUE, Z., SUDDATH, W. O., SATLER, L. F., KENT, K. M., LINDSAY, J., PICHARD, A. D. & WAKSMAN, R. 2010. Impact of chronic obstructive pulmonary disease on acute-phase outcome of myocardial infarction. *Am J Cardiol*, 106, 305-9.
- WALSH, E. E., FALSEY, A. R. & HENNESSEY, P. A. 1999. Respiratory syncytial and other virus infections in persons with chronic cardiopulmonary disease. *Am J Respir Crit Care Med*, 160, 791-5.
- WALTERS, J. A., GIBSON, P. G., WOOD-BAKER, R., HANNAY, M. & WALTERS, E. H. 2009. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD001288.
- WALTERS, J. A., SMITH, S., POOLE, P., GRANGER, R. H. & WOOD-BAKER, R. 2011a. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD001390.
- WALTERS, J. A., TAN, D. J., WHITE, C. J., GIBSON, P. G., WOOD-BAKER, R. & WALTERS, E. H. 2014a. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 9, CD001288.
- WALTERS, J. A., TAN, D. J., WHITE, C. J. & WOOD-BAKER, R. 2014b. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 12, CD006897.
- WALTERS, J. A., TURNOCK, A. C., WALTERS, E. H. & WOOD-BAKER, R. 2010. Action plans with limited patient education only for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, CD005074.
- WALTERS, J. A., WALTERS, E. H., NELSON, M., ROBINSON, A., SCOTT, J., TURNER, P. & WOOD-BAKER, R. 2011b. Factors associated with misdiagnosis of COPD in primary care. *Prim Care Respir J*, 20, 396-402.
- WEDZICHA, J. A., CALVERLEY, P. M., SEEMUNGAL, T. A., HAGAN, G., ANSARI, Z. & STOCKLEY, R. A. 2008. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med*, 177, 19-26.
- WEDZICHA, J. A., DECRAMER, M., FICKER, J. H., NIEWOEHNER, D. E., SANDSTROM, T., TAYLOR, A. F., D'ANDREA, P., ARRASATE, C., CHEN, H. & BANERJI, D. 2013. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med*, 1, 199-209.
- WEISBERG, J., WANGER, J., OLSON, J., STREIT, B., FOGARTY, C., MARTIN, T. & CASABURI, R. 2002. Megestrol acetate stimulates weight gain and ventilation in underweight COPD patients. *Chest*, 121, 1070-8.
- WEITZENBLUM, E., SAUTEGEAU, A., EHRHART, M., MAMMOSSER, M. & PELLETIER, A. 1985. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*, 131, 493-8.

- WELLS, J. M., WASHKO, G. R., HAN, M. K., ABBAS, N., NATH, H., MAMARY, A. J., REGAN, E., BAILEY, W. C., MARTINEZ, F. J., WESTFALL, E., BEATY, T. H., CURRAN-EVERETT, D., CURTIS, J. L., HOKANSON, J. E., LYNCH, D. A., MAKE, B. J., CRAPO, J. D., SILVERMAN, E. K., BOWLER, R. P. & DRANSFIELD, M. T. 2012. Pulmonary arterial enlargement and acute exacerbations of COPD. *N Engl J Med*, 367, 913-21.
- WELSH, E. J., CATES, C. J. & POOLE, P. 2013. Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 5, CD007891.
- WELTE, T., MIRAVITLLES, M., HERNANDEZ, P., ERIKSSON, G., PETERSON, S., POLANOWSKI, T. & KESSLER, R. 2009. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 180, 741-50.
- WHITTAKER, R., MCROBBIE, H., BULLEN, C., BORLAND, R., RODGERS, A. & GU, Y. 2012. Mobile phone-based interventions for smoking cessation. *Cochrane Database Syst Rev*, 11, CD006611.
- WILDMAN, M. J., SANDERSON, C. F., GROVES, J., REEVES, B. C., AYRES, J. G., HARRISON, D., YOUNG, D. & ROWAN, K. 2009. Survival and quality of life for patients with COPD or asthma admitted to intensive care in a UK multicentre cohort: the COPD and Asthma Outcome Study (CAOS). *Thorax*, 64, 128-32.
- WILKINSON, T. M., DONALDSON, G. C., HURST, J. R., SEEMUNGAL, T. A. & WEDZICHA, J. A. 2004. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 169, 1298-303.
- WILLIAMS, J. E., GREEN, R. H., WARRINGTON, V., STEINER, M. C., MORGAN, M. D. & SINGH, S. J. 2012. Development of the i-BODE: validation of the incremental shuttle walking test within the BODE index. *Respir Med*, 106, 390-6.
- WILLIAMS, J. H., JR. & MOSER, K. M. 1986. Pneumococcal vaccine and patients with chronic lung disease. *Ann Intern Med*, 104, 106-9.
- WILSON, D. H., WAKEFIELD, M. A., STEVEN, I. D., ROHRSCHEIM, R. A., ESTERMAN, A. J. & GRAHAM, N. M. 1990. "Sick of Smoking": evaluation of a targeted minimal smoking cessation intervention in general practice. *Med J Aust*, 152, 518-21.
- WILSON, R. 1998. The role of infection in COPD. *Chest*, 113, 242S-248S.
- WILT, T. J., NIEWOEHNER, D., KIM, C., KANE, R. L., LINABERY, A., TACKLIND, J., MACDONALD, R. & RUTKS, I. 2005. Use of spirometry for case finding, diagnosis, and management of chronic obstructive pulmonary disease (COPD). *Evid Rep Technol Assess (Summ)*, 1-7.
- WISE, R. A., ANZUETO, A., COTTON, D., DAHL, R., DEVINS, T., DISSE, B., DUSSE, D., JOSEPH, E., KATTENBECK, S., KOENEN-BERGMANN, M., PLEDGER, G. & CALVERLEY, P. 2013. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med*, 369, 1491-501.
- WONG, C. X., CARSON, K. V. & SMITH, B. J. 2012. Home care by outreach nursing for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 4, CD000994.
- WORLD HEALTH ORGANIZATION 1999. Tobacco Free Initiative: Policies for Public Health. Geneva: World Health Organization.
- WU, T. C., HUANG, Y. C., HSU, S. Y., WANG, Y. C. & YEH, S. L. 2007. Vitamin E and vitamin C supplementation in patients with chronic obstructive pulmonary disease. *Int J Vitam Nutr Res*, 77, 272-9.
- XU, W., COLLET, J. P., SHAPIRO, S., LIN, Y., YANG, T., PLATT, R. W., WANG, C. & BOURBEAU, J. 2008. Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations. *Am J Respir Crit Care Med*, 178, 913-20.
- YANG, I. A., CLARKE, M. S., SIM, E. H. & FONG, K. M. 2012. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 7, CD002991.
- YEH, S. S., DEGUZMAN, B. & KRAMER, T. 2002. Reversal of COPD-associated weight loss using the anabolic agent oxandrolone. *Chest*, 122, 421-8.
- YELLOWLEES, P. M., ALPERS, J. H., BOWDEN, J. J., BRYANT, G. D. & RUFFIN, R. E. 1987. Psychiatric morbidity in patients with chronic airflow obstruction. *Med J Aust*, 146, 305-7.
- YOHANNES, A. M. & ERSHLER, W. B. 2011. Anemia in COPD: a systematic review of the prevalence, quality of life, and mortality. *Respir Care*, 56, 644-52.
- YOHANNES, A. M., WILLGOSS, T. G. & VESTBO, J. 2011. Tiotropium for treatment of stable COPD: a meta-analysis of clinically relevant outcomes. *Respir Care*, 56, 477-87.

- YOUNG, I. H., CROCKETT, A. J. & MCDONALD, C. F. 1998. Adult domiciliary oxygen therapy. Position statement of the Thoracic Society of Australia and New Zealand. *Med J Aust*, 168, 21-5.
- ZHENG, J. P., KANG, J., HUANG, S. G., CHEN, P., YAO, W. Z., YANG, L., BAI, C. X., WANG, C. Z., WANG, C., CHEN, B. Y., SHI, Y., LIU, C. T., CHEN, P., LI, Q., WANG, Z. S., HUANG, Y. J., LUO, Z. Y., CHEN, F. P., YUAN, J. Z., YUAN, B. T., QIAN, H. P., ZHI, R. C. & ZHONG, N. S. 2008. Effect of carbocysteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. *Lancet*, 371, 2013-8.
- ZHENG, J. P., WEN, F. Q., BAI, C. X., WAN, H. Y., KANG, J., CHEN, P., YAO, W. Z., MA, L. J., LI, X., RAITERI, L., SARDINA, M., GAO, Y., WANG, B. S. & ZHONG, N. S. 2014. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. *Lancet Respir Med*, 2, 187-94.
- ZHOU, Y., WANG, X., ZENG, X., QIU, R., XIE, J., LIU, S., ZHENG, J., ZHONG, N. & RAN, P. 2006. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. *Respirology*, 11, 603-10.
- ZIELINSKI, J., TOBIASZ, M., HAWRYLKEWICZ, I., SLIWINSKI, P. & PALASIEWICZ, G. 1998. Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. *Chest*, 113, 65-70.
- ZIGMOND, A. & SNAITH, R. 1983. The hospital anxiety and depression scale. *Acta Psychiatr Scand*, 67, 361-70.
- ZWAR N, R. R., BORLAND R, STILLMAN S, CUNNINGHAM M, LITT J 2004. Smoking cessation guidelines for Australian general practice: practice handbook. In: AGEING, D. O. H. A. (ed.). Canberra: Australian Government Department of Health and Ageing.
- ZWAR, N. A., MARKS, G. B., HERMIZ, O., MIDDLETON, S., COMINO, E. J., HASAN, I., VAGHOLKAR, S. & WILSON, S. F. 2011. Predictors of accuracy of diagnosis of chronic obstructive pulmonary disease in general practice. *Med J Aust*, 195, 168-71.
- ZWAR, N. A., MENDELSON, C. P. & RICHMOND, R. L. 2014. Supporting smoking cessation. *BMJ*, 348, f7535.
- ZWERINK, M., BRUSSE-KEIZER, M., VAN DER VALK, P. D., ZIELHUIS, G. A., MONNINKHOF, E. M., VAN DER PALEN, J., FRITH, P. A. & EFFING, T. 2014. Self management for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 3, CD002990.