

**The Impact of Long Term Oxygen Therapy on South Australian
Patients with Chronic Lung Disease.**

Alan Joseph Crockett PSM, MPH

Department of General Practice

Faculty of Health Sciences

The University of Adelaide, Adelaide, South Australia

September 2005

STATEMENT OF ORIGINALITY

This thesis contains material that has been published in peer-reviewed scientific journals. I have acted as the principal author of the scientific publications that form the main body of the thesis.

This work has not been accepted for the award of any other degree or diploma in any other University or tertiary institution. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to a copy of this thesis being made available for loan and photocopying following its deposition in the University Library.

18. 8. 2005

Alan J Crockett

18th August, 2005

ACKNOWLEDGEMENTS.

I have had an extremely fortunate working life and there are many who deserve my thanks and acknowledgement for the role they played in developing my career.

To begin with, it was the late Drs Brian Hartnett and Alastair H Campbell who gave me my first opportunity to work in the field of respiratory physiology 40 years ago at the Repatriation General Hospital, Concord. To both of them I owe a debt of gratitude for opening up to me the world of respiratory medicine and clinical research.

It was during my time at Concord that I first came under the influence of the late Professor Ann Woolcock. I have tried to fulfil all the lessons and challenges that she presented. I have become a better scientist for her efforts.

It was Dr Bill Leckie and the late Geoff Ey who enticed me to South Australia. I thank them both for the friendship and trust they placed in me. Not long after arriving in South Australia Professor John Chalmers enticed me to the new medical school at Flinders University and Flinders Medical Centre. Emeritus Professor John ("Jack") Alpers became my director and in the ensuing 30 years became a close friend and mentor. None of the work presented in this thesis would have been possible if it had not been for their encouragement and support.

Jo Cranston needs special mention. Jo has responded to all my ideas for our research collaborations for the majority of the publications presented in this publication. She has diligently collected the data, created databases and drafted the papers. I owe her a sincere debt of gratitude.

John Moss taught me health economics and prompted me to become interested in health technology assessment and resource allocation. I have greatly enjoyed and appreciated our collaborations over the years. Thank you.

Professor Richard Ruffin who I first worked with at Flinders Medical Centre and Professor Justin Beilby have both given generously their time and expertise in reviewing this work as my supervisors. I also thank Justin for introducing me to primary health care in my 'retirement'. Dick Ruffin initially provided enormous support and training at Flinders in the early days and more recently has lent me his critical eye and ears: thank you!

I would like to sincerely thank all those patients who over the 40 years of working in the field of respiratory medicine have shared with me their experience of lung disease and in particular how long term oxygen therapy impacted on their life.

Gillian Laven also needs special mention, as she was responsible for bringing to my attention the possibility of obtaining a PhD by prior publication. All I can say is thank you!

Finally, the two most important people in my life, Kathy, my wife and partner for 40 years and Fiona our daughter, both have always been there for me. None of what I have achieved in my life would have been possible without their love and support. I offer them my heartfelt gratitude and my love.

STATEMENT OF ORIGINALITY	2
ACKNOWLEDGEMENTS.	3
ABSTRACT	7
CHAPTER 1.....	12
Introduction.....	12
Defining COPD.....	14
Natural history of COPD.....	18
Symptoms	20
End Stage COPD	21
Classification of respiratory failure.....	21
Epidemiology In Australia.....	22
Prevalence in Indigenous Australians	25
Economic Impact.....	25
Direct Costs.....	29
Indirect Costs	33
Total cost.....	34
Home oxygen therapy	36
CHAPTER 2.....	42
Literature Review	42
Historical Aspects of Oxygen Therapy.....	42
CHAPTER 3.....	66
Oxygen concentrators--an economical new technology	66
CHAPTER 4.....	71
Cost Centre Management: How it Helped Reduce Home Oxygen Costs. 71	
The continuing impact of home oxygen therapy for respiratory patients on a hospital budget.	73
CHAPTER 5.....	79
Home oxygen therapy: an audit of survival	79
CHAPTER 6.....	86
Trends in chronic obstructive pulmonary disease mortality in Australia. ...	86
CHAPTER 7.....	90
The effects of home oxygen therapy on hospital admission rates in chronic obstructive airways disease.....	90
Initial trends in quality of life and survival in CAL patients on domiciliary oxygen therapy.....	93

Monaldi Archives of Chest Disease 1996; 51(1): 64-71	93
Effects of long-term oxygen therapy on quality of life and survival in chronic airflow limitation.....	97
Monaldi Archives of Chest Disease 1999; 54(2): 193-196	97
Non-conventional indications of long-term oxygen therapy: oxygen therapy during exercise.....	100
CHAPTER 8	120
The MOS SF-36 health survey questionnaire in severe chronic airflow limitation: a comparison with the Nottingham Health Profile.....	120
CHAPTER 9	128
Program budgeting and marginal analysis: a case study in chronic airflow limitation.....	128
CHAPTER 10	143
Domiciliary oxygen for chronic obstructive pulmonary disease	143
Cochrane Database of Systematic Reviews 2000(4): CD001744	143
CHAPTER 11	165
An association between length of stay and co-morbidity in chronic airflow limitation	165
CHAPTER 12	174
Survival on long-term oxygen therapy in chronic airflow limitation: from evidence to outcomes in the routine clinical setting.....	174
CHAPTER 13	185
The impact of anxiety, depression and living alone in chronic obstructive pulmonary disease.....	185
CHAPTER 14	196
The relative survival of COPD patients on long-term oxygen therapy in Australia	196
CHAPTER 15	205
Conclusion.....	205
Recommendations	209
BIBLIOGRAPHY	224
APPENDICES Examples of Citations	235

ABSTRACT

The peer-reviewed publications contained within this thesis describe studies that have contributed significantly to the understanding of long-term oxygen therapy (LTOT) for Australian Chronic Obstructive Pulmonary Disease (COPD) patients. My personal contribution to each of these studies ranged from the initial development of the hypotheses and design and execution of the investigations, submission of research grants applications to fund the studies through to preparation of the manuscripts for publication.

When LTOT was first introduced into Australia I was fortunate to meet the key experts in LTOT including Professors Tom Petty, Nick Anthonisen, David Flenley, Pierre Levi-Valensi and Peter Howard. At that time all were involved in randomised controlled trials of oxygen therapy. (1, 2), 3). I also visited several oxygen concentrator and oxygen supply companies in the USA and UK. It was during these visits that I became convinced that the concentrator provided a more economical and efficient method of LTOT delivery.

In 1980, an oxygen concentrator was imported to Australia by the spouse of one of our patients suffering from emphysema who was receiving long term oxygen via cylinders. In 1982, two oxygen concentrators were donated to FMC by two different manufacturers (DeVilbiss and Marx) based in the USA. These instruments were trialled on a male and female patient receiving LTOT in the Southern Adelaide metropolitan area. The initial acceptance of this device by these patients led to a submission to the South Australian Department of Health for a grant to purchase 40 units. Funds were finally obtained for the purchase of 34 concentrators by FMC and these were rolled out to the then existing patients who were receiving LTOT in 1984.

Up to this point in time the only published guidelines or recommendations for LTOT came from the American College of Chest Physicians in 1973(3) and the American Thoracic Society in

1977(4). In 1982, the staff of the Respiratory Unit, FMC held a workshop where it was agreed that patients' would be assessed for home oxygen therapy using the 1977 American Thoracic Society Guideline.

The late Professor Ann Woolcock presented a paper during a 1983 symposium titled "Long Term Oxygen Therapy: A World View" during a 1983 symposium held in Toronto, Canada where she estimated that at that time 2,100 patients were receiving oxygen in New South Wales for an average of 1 hour per day. She further reported that the use of cylinders ranged from 1 cylinder a year to 14 cylinders per week. Physicians were reported to have been conservative in their approach to oxygen therapy and that only 50 people were on long term oxygen therapy in New South Wales. Presumably the vast majority of these patients were receiving intermittent oxygen therapy. Woolcock mentioned that oxygen concentrators were available but provided no specific detail of their use in Australia(5).

The first Australian guideline for the provision of domiciliary long-term oxygen therapy appeared in 1985. This guideline was developed at the request of the Thoracic Society of Australia and New Zealand.(6). In the same year I published my first paper relating to the provision of oxygen therapy via an oxygen concentrator based on our initial experiences with this technology(7). In the following year I published a paper documenting the analysis of the costs for providing home oxygen therapy. I also reported how Cost-Centre Management led to the introduction of practical measures for improved clinical decision making and improved expenditure control resulting in substantial cost savings(8). This publication led to a paper reporting the rationalization of the supply of home oxygen in the Hunter region of New South Wales.(9). This paper also reported the one to five year survival rates for their patients. At that time only between 5 and 12% of patients were receiving LTOT oxygen via an oxygen concentrator.

At best, oxygen therapy is cumbersome with the patient 'tethered' to the oxygen source that, in the past, limited the movement of the patient due to the size and weight of the oxygen cylinders. Oxygen concentrators provided a partial answer to these problems.

The introduction of this new technology led to ongoing evaluation of the impact on patient care and acceptance of the intervention and whether the expected outcomes increased survival and quality of life, were achieved(10). In 1991 I published the first detailed Australian data on survival for patients receiving home oxygen therapy. The results of this study indicated that the mortality rate for COPD with respiratory failure at 1 year was twice the rate reported by the Medical Research Council Working Party and the Nocturnal Oxygen Therapy multicentre trials. This was in spite of the baseline physiological parameters for our patients being similar to the patients in these benchmark studies. I was later able to show that survival of our long term oxygen patients was no better than the control group of the original MRC study(11-13). The second significant observation was that females survived longer than males(14).

In 1992 a further paper was published and reported that in spite of strict prescription criteria and the introduction of a cost-saving new technology oxygen concentrators, the budget for this intervention remained under pressure. This was largely due to a rapidly increasing demand from eligible patients(10). A further analysis of the longitudinal data resulted in a report of an association between home oxygen therapy with a reduction in respiratory admissions and bed days(15).

At this time there was a relative paucity of information about the trends of mortality in COPD in Australia. To further understand the burden of disease (COPD) and changing trends in mortality over time a research project was undertaken that indicating that the mortality of females from COPD was increasing whilst it was decreasing in males(16).

The relatively poor survival outcomes for our home oxygen patients prompted further attempts to understand the costs and benefits in terms of quality of life and the evaluation of two generic health related quality of life questionnaires available at that time (1996). The results of the study suggested that the sole use of the SF-36 as a health outcome measure in COPD patients might fail to provide information about the mental domains of their quality of life. Decreased cognitive function, anxiety and depression were shown in Australian COPD patients(17).

A series of papers published in Europe describing the observations made on Australian home oxygen patients were published between 1996 and 2000 at the request of the International Oxygen Club. The membership of this club included Professors Tom Petty, David Flenley , Pierre Levi-Valensi, Peter Howard, Heinrich Matthys and Roland Keller(11, 18, 19, 20). Further attempts to rationally allocate resources in the management of COPD in the acute care setting were reported in 1999 using Program Budgeting and Marginal Analysis.(21).

I undertook a systematic Cochrane Review of the five randomized controlled trials of the use of home or long term oxygen therapy in COPD demonstrating that this intervention improved survival in a selected group of severely hypoxaemic COPD patients (22). However, this intervention does not appear to provide any benefit for patients with moderate hypoxaemia or nocturnal desaturation. (20) This review has been translated into several languages and is cited as the basis of many of the more recent guidelines regarding LTOT.

More recently a NH&MRC funded study report was published reviewing the impact of evidence based clinical practice concerning LTOT. This report resulted in several peer reviewed papers being published where we explored the relationship between the evidence and the observed outcomes in terms of both survival and quality of life(13, 23, 24).

Finally, we conducted a study of the relative survival of our patients compared to those patients with similar characteristics in France. We demonstrated that our patients' relative survival was less than their French counterparts(25). At the time of publication this was only the second paper to be ever-published using relative survival analysis in COPD and the first in Australia. This difference is hard to explain by the level of severity, number of pack years or level of lung function impairment. Other possible factors contributing to the excess mortality in South Australian COPD patients need to be investigated.

CHAPTER 1

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is recognised as one of the major global public health problems with substantial morbidity and economic burdens. It is one of the few chronic diseases that is an increasing cause of mortality and morbidity worldwide(26). The international Global Burden of Disease Study has estimated that from 1990 to 2020 COPD would increase worldwide from firstly, the sixth leading cause of death to the third leading cause of mortality and secondly, from the twelfth to the fifth leading cause of disability adjusted life years lost(27). COPD is also a major cause of mortality and morbidity in Australia. Chronic airflow limitation that is associated with COPD and allied diseases was the fourth highest cause of death in Australia in 1996, behind cancer, ischaemic heart disease and cerebrovascular disease, and accounted for 5.4% of all deaths.

The end-stage of COPD generally results in repeated episodes of respiratory failure often related to acute exacerbations of the underlying disease, acute respiratory infection or exposure to pollution. Respiratory failure is defined as hypoxaemia ($\text{PaO}_2 < 60 \text{ mm Hg}$) and in some cases combined with hypercarbia ($\text{PaCO}_2 > 50 \text{ mm Hg}$). Hypoxaemia is often present continuously in chronic respiratory failure due to end-stage COPD. Corrections of hypoxaemic episodes underpin the treatment of this condition(28).

There are four certain characteristics that are important from a physician's perspective. Firstly, the condition must cause the patient symptoms since curing an asymptomatic patient is not very gratifying. Secondly, it must be difficult to diagnose as the satisfaction of making the correct diagnosis in spite of all those physicians who preceded you are many. Thirdly, the disease must be severe enough to threaten death or disability if not correctly diagnosed. Fourthly, the condition must be curable or at least treatable. Hypoxaemia might at first seem to

meet all these criteria. Hypoxaemic patients are usually symptomatic but the underlying source of their symptoms may not be readily apparent. The condition can be severely debilitating and often fatal. Hypoxaemia is usually easily treatable with supplemental oxygen.

This thinking is at best simplistic. Hypoxaemia is not a disease of itself, but rather a proximate manifestation of any number of disease processes. Whether the underlying condition is acute and potentially reversible, such as pneumonia, or chronic, progressive and largely incurable, like COPD, the presence of hypoxaemia is a marker of the severity of the illness. If COPD is so advanced as to cause hypoxaemia, there is significant organ dysfunction and the condition is by definition severe. However, whilst hypoxaemia is only a marker of an illness process, it is a treatable marker. The underlying COPD may not change, but the deficit that has resulted from this condition, a deficit of oxygen in the bloodstream, is reversible merely by replacement therapy (29).

Defining COPD

COPD has had many names in the past 50 years including: *Chronic Obstructive Airways Disease* (COAD); *Chronic Obstructive Lung Disease* (COLD); *Chronic Airflow Limitation* (CAL or CAFL); and *Chronic Airflow Obstruction*. COPD as we currently understand it comprises two related diseases, *chronic bronchitis* and *emphysema*, one rarely occurring without a degree of the other. Therefore, COPD is seen to be a collective term for chronic bronchitis and emphysema. The definition of COPD that is currently accepted internationally, is summarized as follows:

"COPD is a chronic disease characterized by progressive airflow obstruction, chronic cough, and dyspnea in advanced stages, caused by smoking, environmental, and hereditary factors" or as the Global Initiative for Chronic Obstructive Lung Disease has expanded to define COPD as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases" (30).

This definition highlights the more recent evidence that there appears to be genetically determined factors that result in between one in five (31) to one in two patients being susceptible to the harmful effects of tobacco smoke.

The problem of classification and definition of the syndromes that lead to chronic airflow limitation (CAL) that is associated with COPD is made complex by many factors because it is a physiological term and therefore requires a measurement of airway function, usually spirometry, for diagnosis. Recently, Hogg (32) offered the following definition: "airflow limitation that defines COPD is the result of a prolonged time constant for lung emptying,

caused by increased resistance of the small conducting airways and increased compliance of the lung as a result of emphysematous destruction".

The word "chronic" also requires some definition. There seems little evidence tying the number of years the symptoms are present for the label "chronic" to be applied to the diagnosis. However, at least one medical dictionary defines chronic as " a disease or disorder developing slowly and persisting for a long period of time, often for the remainder of the lifetime of an individual." This accurately describes the aetiology and prognosis of COPD(33).

Charles Badham adopted the term to define "chronic pectoral (chest) complaints, especially those of people advanced in life". He recognized that chronic bronchitis was a serious and disabling disorder in 1808 (34). In 1819, Laennec (35) invented the stethoscope, which became the first instrument by which lung structure and function could be indirectly studied. Laennec first described the symptoms and physical signs of emphysema in his treatise of disease of the chest, in 1827 (35). John Hutchinson (36) invented the spirometer in 1846. Today a spirometer is the key instrument to diagnosing COPD and its severity and to assessing responses to therapy.

In 1944, Christie suggested that, "The diagnosis should only be considered certain when dyspnea on exertion, of insidious onset, not due to bronchospasm, or left ventricular failure, appears in a patient who has some of the physical signs of emphysema together with chronic bronchitis or asthma" (37). Oswald et al (38) described the clinical features of 1,000 cases of chronic bronchitis in 1953. Two landmark conferences, the CIBA Guest Symposium (39) and the American Thoracic Society Symposium (40) developed the first agreed-on definitions of chronic bronchitis and emphysema in 1959 and 1962, respectively. By 1966, Burrows et al (41) offered a unifying hypothesis to reconcile the differences between British chronic bronchitis and American emphysema. Both experts concluded that patients in the United

Kingdom and the United States shared common features of both chronic bronchitis and emphysema (41). They suggested that the spectrum should be called chronic obstructive lung or pulmonary disease, GOLD or COPD. The latter has generally been adopted as the universal acronym. The working definition for COPD that was used in the 1970s might be summarized as follows: "COPD is a mixture of chronic bronchitis and emphysema. It is associated with smoking and is characterized by cough and dyspnea, and premature morbidity and mortality".

The landmark study by Hogg et al (42) in 1968 ushered in the era of small airways disease. By the 1980s, the clinical spectrum of COPD was known to cover a 30-year process and wore the labels of chronic bronchitis, asthmatic bronchitis, and emphysema. The working diagnosis of COPD in 1980 was "COPD is a smoker's disease with progressive airflow obstruction, which clusters in families and worsens with age".

This diagnosis of chronic bronchitis or chronic mucus hyper secretion is usually made clinically or from questionnaire data. It is based on the MRC questionnaire and is most commonly made when a cough with sputum is present for more than 3 months of a year for two consecutive years when other causes for these symptoms can be excluded. A chronic productive cough probably begins about 15 years after starting regular smoking(43). Whilst this method of definition leads to a division between "positive" and "negative" the distribution of morphologic bronchial mucous gland size in the population appears to be unimodal (44). Therefore, differentiation at that time rested on an insecure morphologic foundation. More recently the work of Hogg (32) and Barnes (45-47) identifying the various mediators involved in both asthma and COPD have done a great deal in clarifying these issues.

The effects of inhaling of cigarette smoke are very complex. The same components of the smoke, there are more than 4,000, may cause different effects at all levels of the airway,

sometimes in varied sequence among individuals. In some individuals these components may have no effect at all. The close association between tobacco smoking and the development of emphysema, chronic bronchitis, and a full spectrum of COPD has been known for many years. Some studies have shown that smoking creates oxidative stress, attracts neutrophils to the lungs, and creates inflammation through a multiplicity of inflammatory cytokines that also involve the CD8 lymphocyte, the alveolar macrophage, the neutrophil, and a multitude of proteases, both those that are neutrophil-derived and those derived from the cells of the bronchial epithelium (45, 48).

Emphysema is a histologically defined entity that can only be diagnosed post-mortem or after surgical intervention. However, imaging with high-resolution computer tomography can support the anatomical basis for the diagnosis of emphysema (49). Accurate diagnosis during life is problematical. The fact that methods or fashions of classification predetermine conclusions has hampered understanding. If radiological criteria are taken to be the sole determinants of the presence of morphological emphysema it is easy to conclude that chronic bronchitis causes most of the disability. Severe chronic bronchitis logically implies more severe mucus hypersecretion. However, what is often meant is worsening airflow limitation and physiological abnormalities such as impaired gas exchange.

Asthma is characterized by 'obstruction to airflow which is variable spontaneously and in response to treatment'. It has also been postulated that poorly controlled asthma over a long period of time, usually measured in decades, results in the obstruction in asthma becoming less reversible (50). Whilst the majority of asthma sufferers are not included under the rubric of COPD, it remains controversial whether those chronic asthmatics whose airways obstruction, has over time, become less reversible should be now classified as having COPD.

Both asthma and COPD have a familial component and are inflammatory and bronchospastic processes. Asthma however, is much more reversible than COPD in its response to therapy, bronchodilators, and corticosteroid drugs. Airflow obstruction in patients with chronic asthma tends to be slowly progressive as a consequence of airway remodeling and fibrosis. By contrast, COPD is much less reversible in response to bronchoactive drugs and tends to be inexorably progressive (50).

Natural history of COPD

The natural history of COPD begins with complex biochemical and cellular events in the small airways and surrounding alveoli. Very soon, damage to the structure leads to a loss of elastic recoil (51). The lungs begin to increase in size, and the FVC may increase. This results in early physiologic alterations that can be readily identified by simple spirometry (52, 53). By the time that both clinical and radiological signs are present, COPD is in a moderate-to-advanced stage.

Pathological evidence of emphysema can be derived from CT studies or from resected material, such as when solitary nodules are removed. The only practical and economical way to diagnose and to assess the progress of COPD is with spirometry. The initial smoking-induced injury to the human lungs appears to be in the small conducting air passages and surrounding alveoli. When alveoli become damaged or lost, the elastic supporting structure of the lung is reduced. This results in both a loss of elastic recoil and in increased airways resistance, since airways are no longer tethered by the radial traction forces of the surrounding alveolar attachments. Mural inflammation of small airways and airways remodeling also reduce the airway lumen and result in increased airway resistance.

Thus, the interrelated causes of airflow obstruction in COPD patients are a combination of airways inflammation and remodeling, bronchospasm, mucous hypersecretion, and loss of

elastic recoil. There is a complex interrelationship among these phenomena, which results in the progressive reduction in expiratory airflow, as judged by FEV₁ values.

It is interesting that early stages of emphysema are characterized by both hyperinflation and an increased FVC (51). This is the reason why the FEV₁/FVC ratio is such an exquisitely sensitive test for early stages of airflow obstruction. An FEV₁/FVC of < 70% heralds the onset of rapid decline in FEV₁ over the course of the next 10-year period (53). Thirty or more years of progressive loss in airflow may take place before the threshold to symptomatic dyspnea on exertion occurs, which is usually at < 1.5 L/s and may be as low as 1.0 L/s in smaller persons.

The aetiological sequence of events leading to COPD has been divided into the "British" and the "Dutch" hypotheses. The "British" hypothesis considered that mucus hyper-secretion which was secondary to tobacco smoking and other environmental or occupational exposures were the initiating stages of COPD. The alternative "Dutch" hypothesis focused on the role of endogenous bronchial hyper-reactivity leading to the development of COPD.(54)

In summary the syndrome of COPD and chronic airflow limitation consists of four potential major components:

- Chronic mucus hypersecretion (a clinical diagnosis based on history).
- Pulmonary emphysema (destruction of parenchyma, a histological diagnosis).
- Airway hyper reactivity (diagnosed with spirometry and bronchial challenge studies).
- Changes in small airways (diagnosed with spirometry or some measures of airways resistance).

It may also result from six additional but less common clinical entities:

- Bronchiectasis and cystic fibrosis.
- Airflow limitation in association with parenchymal fibrosis or granulomatosis.
- Pulmonary lymphangiomyomatosis.
- Tracheal stenosis and large airway obstruction.
- Syndrome of chronic bronchiolitis either associated with rheumatoid disease or as a primary condition.
- Poorly treated asthma.

Symptoms

The cardinal symptom of COPD is dyspnoea, which is of varying intensity in those patients who have varying airways obstruction, but which is progressive and unvarying in those with advanced emphysema. Kinsman and colleagues asked patients with chronic bronchitis and emphysema to rate the frequency of symptoms and experiences. In decreasing order of frequency were dyspnoea, fatigue, sleep disturbances, congestion, irritability, anxiety, loss of interest, poor appetite, helplessness/hopelessness, poor memory and feelings of alienation (55).

Many of these symptoms may be caused by hypoxia, particularly loss of memory, sexual dysfunction and weight loss (56). However, there have been no studies as yet demonstrating a close relationship between the symptoms and the arterial PaO₂. The greater degree of emphysema the more severe were the symptoms relating to loss of interest in life (57).

Physicians, nurses and allied health professionals often find the early diagnosis and differentiation of obstructive airway diseases to be a challenging problem. The history and

physical examination are often not enough to detect either the presence of, or determine the type of, lung disease present.

End Stage COPD

The end-stage of COPD generally results with repeated episodes of respiratory failure often related to acute exacerbations of the underlying disease, acute respiratory infection or exposure to pollution(28). The term respiratory failure acquired a precise meaning as a result of the improved understanding of respiratory physiology that resulted from the demands of aviation during the Second World War (58). Sykes, McNicol and Moran Campbell recommended only two situations where oxygen therapy may be used. The first and most obvious is in the resuscitation of an apnoeic patient. The second is in the relief of hypoxaemia that results from hypoventilation, ventilation perfusion inequalities and right-to-left shunts that are associated with respiratory failure.

Classification of respiratory failure

Respiratory failure may be classified as hypoxaemic or hypercapnic and may be either acute or chronic. Hypoxemic respiratory failure (type I) is characterized by a PaO_2 of less than 60 mm Hg with a normal or low PaCO_2 (58). This is the most common form of respiratory failure, and it can be associated with virtually all acute diseases of the lung, which generally involve fluid filling or collapse of alveolar units. Some examples of type I respiratory failure are cardiogenic or non-cardiogenic pulmonary oedema, pneumonia, and pulmonary haemorrhage (58).

Hypercapnic respiratory failure (type II) is characterized by a PaCO_2 of more than 50 mm Hg (58). Hypoxemia is also present in patients with hypercapnic respiratory failure who are breathing room air. The pH depends on the level of bicarbonate, which, in turn, is dependent

on the duration of hypercapnia. Common aetiologies include drug overdose, neuromuscular disease, chest wall abnormalities, and severe airway disorders (eg, asthma, COPD).

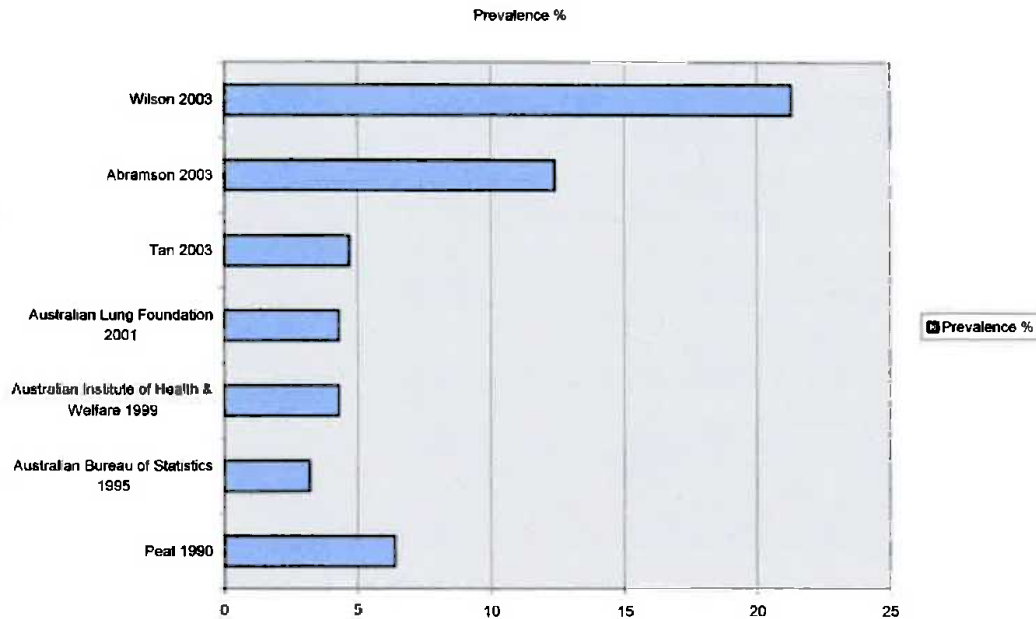
Oxygen therapy is generally introduced once significant hypoxaemia is diagnosed. That is, an arterial oxygen tension of less than 55 mm Hg is present at rest. This stage of COPD is frequently labelled 'end-stage' as the long-term survival of the patient is generally limited.

Epidemiology in Australia

COPD is a major cause of mortality and morbidity in Australia. Chronic airflow limitation that is associated with COPD and allied diseases were the fourth highest cause of death in Australia in 1996, behind cancer, ischaemic heart disease and cerebrovascular disease, and accounted for 5.4% of all deaths. It has been estimated that approximately 37.5 persons per 1,000 Australian population are suffering from either chronic bronchitis or emphysema although the underlying burden of this disease has not been fully identified in Australia(59). An increasing number of females are being diagnosed with COPD. Although male age-standardised mortality for COPD has declined in recent years, female mortality increased 2.6 fold from 1964 to 1990(16). The mortality rate in females is expected to equal male mortality by about the year 2005. In 1997 it was reported that the Australian age-standardised mortality rate for COPD per million population was 409.1 for males and 173.5 for females, almost double that reported for the rest of the world (males 237.7, females 106.8 per million population) although the reason for this has not been determined(60). The U.S. Surgeon General reported that a long history of cigarette smoking is the most salient feature of the aetiology of the disease (61). It is not clear why such large differences between countries should exist. The differences in the mortality between the United States, Canada and the British Isles from chronic bronchitis, COPD and emphysema appear to be real (51).

The measurement of the overall prevalence of COPD and comparison of rates depends on several factors including diagnostic criteria, comorbidities, age of the survey sample and changing International Classifications of Diseases codes. In 1990, Wilson reported that COPD occurred in 24% of males, 18% of females who were regular smokers and 5% of males and 8% of females who were reported to be non-smokers (62). In 1996, the Australian Institute of Health and Welfare estimated a prevalence of 300,000 persons with COPD with 20,000 new cases annually. Extrapolating this data gives an estimated 380,000 persons with COPD in 2000. Recently, 12.4% of postal survey respondents aged 45-70 years, self-reported chronic bronchitis or emphysema (63, 64). Therefore, it can be estimated that the prevalence for COPD in the year 2000 was approximately 620,414 people in this age group. Tan has developed a prevalence estimation model based on European data that has projected an estimated 4.7% (558,000 cases) of the population aged over 30 years with moderate to severe COPD in 2000 (65). A recent study using spirometry estimated a prevalence of mild, moderate and severe COPD of 24.1% of a random population of adults aged over 18 years (62). Extrapolation of these latter figures suggests that there may be as many as 1.2 million persons aged 45-70 years or 2.6 million persons aged over 30 years with COPD in the year 2000. Substantial differences are apparent in prevalence estimates based on self-report of symptoms, medical diagnosis or spirometry.

Table 1. Estimates of the prevalence of COPD in Australia



The number of people suffering from COPD in Australia is not known. Any measured prevalence of COPD will depend on several factors such as diagnostic criteria, confounding medical conditions, the need to make age adjustments, and adjustments for changing revisions to the International Classifications of Diseases (ICD) codes.(66) There are currently several widely different prevalence estimates for COPD in Australia.

The AIHW estimated there were almost 300,000 persons with COPD in 1996 with more than 20,000 new cases annually (67). Recently, 12.4% of a random sample of adults aged between 45-70 responding to a postal survey conducted by the Monash Medical School and the Alfred Hospital self-reported chronic bronchitis or emphysema.(64) Extrapolating this percent prevalence to the total Australian population aged between 45-70 years gives an estimated 620,414 people with COPD in Australia in this age group based on the population at 30 June 2000.

A prevalence estimation model has been applied to estimate the prevalence of COPD in twelve Asia-Pacific countries including Australia. The model produced an estimated

prevalence of COPD of 6.3% for the twelve countries. The report goes on to estimate the number of moderate to severe cases of COPD in Australia at 4.7% of the population aged greater than 30 years (558,000 cases) in the year 2000 (68).

A population-based assessment model developed by Boehringer Ingelheim and applied to the Australian population provides an estimate for the number of moderate to severe cases of COPD in the year 2000 of 474,000 (65). The Busselton study estimated that chronic airflow limitation occurred in 24% of men and 18% of women who were regular smokers and 5% of male and 8% of female non-smokers (69).

Prevalence in Indigenous Australians

Chronic lung disease is a major cause of mortality and morbidity in indigenous Australians. Indigenous Australians die from COPD at a rate 10 times greater than non-indigenous Australians (70). High smoking rates (56.1% males and 48.3% females) (71) and high rates of infectious disease amongst indigenous Australians will continue to contribute to this high mortality rate for many years in the future. A recent study of 244 indigenous Australians in the Northern Territory reported that COPD was generally unrecognised by health providers only being documented in the health record of 8% of those with COPD (72). Chronic respiratory symptoms of chronic bronchitis and recent wheeze were poor predictors of airflow obstruction giving support for community-wide spirometry screening. This is particularly the case in communities with a high prevalence of respiratory disease and tobacco use.

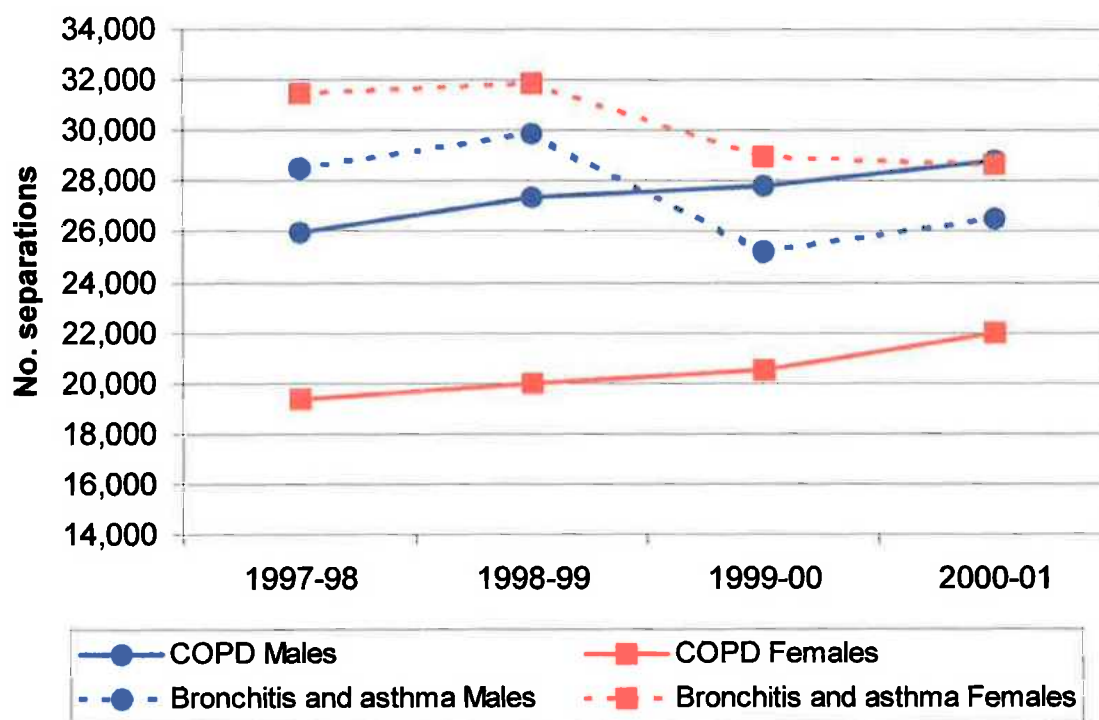
Economic Impact

The prediction that COPD will rise to be the third leading cause of death worldwide by the year 2020 has enormous implications for economic management of healthcare. Current prevalence estimates are likely to be underestimates, as the disease is often not diagnosed until late in its course when lifestyle is significantly impaired. With the ageing population and the

improvement in treating other chronic diseases, the burden of COPD is likely to continue to increase even if the prevalence of cigarette smoking continues to decrease.

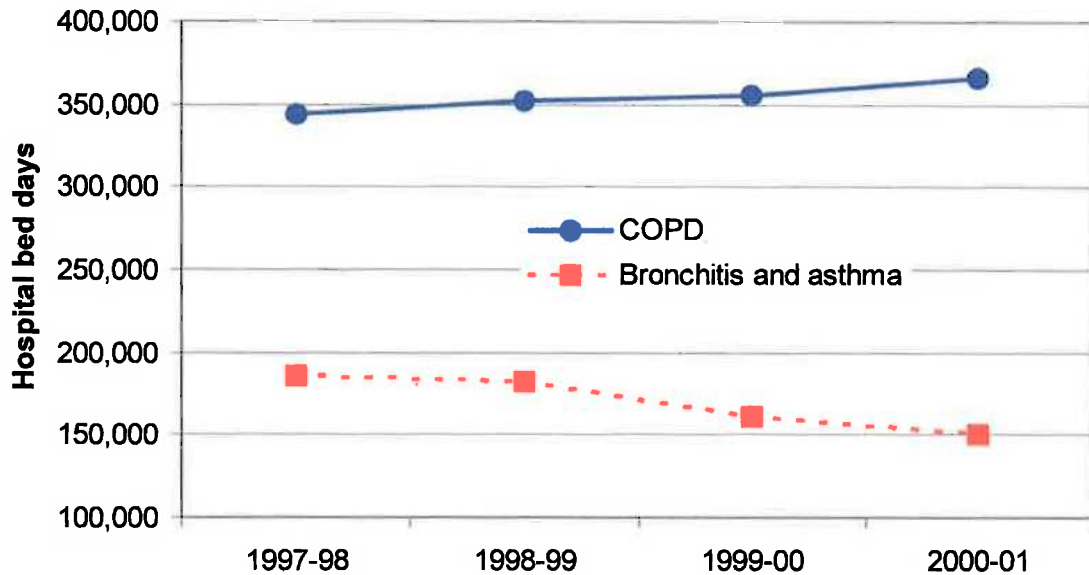
In 2000-01, COPD (E65A and E65B) accounted for 50,779 separations (0.85% of all separations for public and private hospitals); 16.9% of all separations for the respiratory system 366,516 bed days with an average length of stay of 7.2 days. In addition in 2000-01 it is estimated that there were: 635,782 (0.7%) visits to GP for COPD. The number of hospital separations for COPD is increasing annually (Figure 1).(73). Males have more hospital admissions for COPD than females. The rate of hospitalisation increased by 11.1% for males and 13.2% for females from 1997-8 to 2000-01. In contrast the rate of hospitalisation for acute bronchitis and asthma decreased by 7.9% over the same period.

Figure 1. Number of hospital separations for COPD and Acute Bronchitis/Asthma 1997-98 to 2000-01 (Data from the AIHW: National Hospital Morbidity Database)



The number of hospital bed days for COPD has increased with the number of hospitalisations (Figure 2). The number of bed days increased by 6.6% for COPD or 2% annually and decreased by 18.9% (over 6% annually) for acute bronchitis/asthma during 1997-98 to 2000-01 period.

Figure 2 Number of hospital bed days from 1997 to 2001



The cost burden associated with COPD is significant. COPD affects patients, caregivers and society as a whole. For persons suffering from the disease it affects not only medical resource use but health status, daily life and activities. Lung disease, and COPD in particular, also affect work productivity, being among the three main causes of lost workdays. However, estimating the economic burden of COPD is difficult, as there is little data on the burden of illness imposed on society.(74) In addition, misdiagnosis, misclassification and masking of the diagnosis by other co-morbid illnesses leads to a major underestimate of the economic burden.

The costs attributable to COPD are not uniform across patients but vary according to health status, gender, and the amount of co-morbid illness. In a recent study of costs incurred by

persons with COPD in the US approximately 20% of persons with COPD accounted for about 74% of total expenditure(74).

Direct Costs

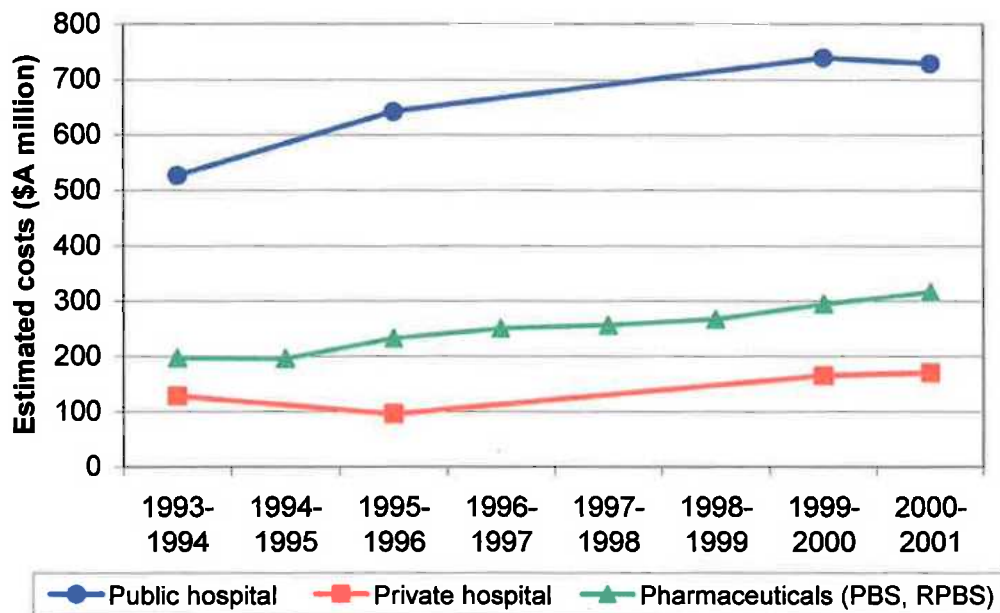
Direct costs are those costs that are directly borne by the health care system to prevent, diagnose and treat illness. The AIHW employed a prevalence-based approach for estimating the direct cost of health services in a major study of health system costs of diseases and injury in Australia for the 1993-94 financial year(75). The methodology used is described in detail according to the major chapter groupings of the Ninth Revision of the International Classification of Diseases (ICD-9) (76). The estimations were based on the estimated resident Australian population by age and sex at 30 June 1994. The AIHW focused on direct costs due to the controversy and debate surrounding the calculation of indirect costs. The information on costs was estimated by detailed health sector for a given disease group defined in terms of a chapter of ICD-9.

In 1993-94 the AIHW estimated the health cost for lung diseases to be \$2.5 billion or 8% of the total health system costs. Lung diseases were the sixth most costly disease group. Hospital cost was the largest contributor to health care costs for lung disease at \$833 million. This estimate included a cost to public hospitals (\$527 million), private hospitals (\$128 million) and for non-inpatients (\$177 million). Total pharmaceutical costs including both prescription and over-the-counter medications were estimated to be \$733 million.

The estimated costs for lung disease for a selected group of healthcare sectors (public hospitals, private hospitals and a combined cost for prescribed pharmaceuticals (Pharmaceutical Benefits Schemes (PBS) and Repatriation Pharmaceutical Benefits Schemes (RPBS)) from 1993-94 to 2000-01 are shown in Figure 3. Costs attributed to lung disease have increased during this time interval by 38.3% for public hospitals, 32.8% for private

hospitals and 60.2% for prescribed pharmaceuticals (75{Australian Institute of Health and Welfare, 2001 #307, 77).

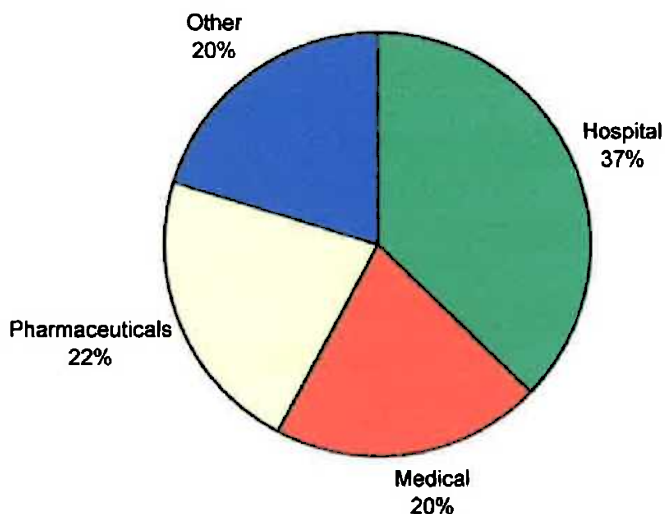
Figure 3. Estimated annual cost (\$A million) for selected health care sectors for lung disease



(Data from AIHW Australia's Health 2002,(78) AIHW Health system costs of diseases and injury and HIC Annual Reports(77) Pharmaceutical and Repatriation Pharmaceutical Benefits Schemes Statistical Tables for each year indicated.)

The AIHW estimated that the cost for COPD alone in 1993-94 was \$300 million, almost three times as much as that for lung cancer.(79) Hospitalisation accounted for the major proportion of costs for COPD (\$112 million) followed by pharmaceutical costs (\$66 million) as shown in Figure 4. The hospitalisation costs for COPD represented 13.4% costs of hospitalisation for all respiratory disease.

Figure 4. Estimated cost of COPD by health sector for 1993-94 (AIHW 1993-94)



In 2000-01 the AIHW estimated the public and private hospital cost for COPD (ICD-10 E65A and E65B) to be \$188 million. This represents a 68% increase from the 1993-94 estimate of hospital costs for COPD(80). The 1993-94 cost attributed to hospitals also included a non-inpatient cost which is not included in the \$188 million hospital cost estimate. Thus the 2000-01 estimated hospital cost for COPD is an underestimate in comparison with the 1993-94 hospital cost. The hospital cost for COPD was the highest hospital cost of any respiratory disease and almost double the estimated hospital cost for asthma of \$95 million in 2000-01. The rate of increase in costs for COPD has exceeded the rate for total lung disease. This is probably due to the ageing population and the increasing mortality and morbidity associated with COPD.

A lack of reliable current prevalence information plus the contribution of co-morbid illness to the overall burden of disease makes the task of estimating the current cost of COPD in Australia extremely difficult. The AIHW estimated direct costs by taking known aggregate expenditures on healthcare and apportioning these to disease categories using known hospital morbidity data, casemix data, the 1990-91 GP survey and the 1989-90 Australian Bureau of Statistics (ABS) and National Health Survey (76). The direct costs calculated did not include costs for ambulance services, health promotion and disease prevention. To gain an insight into the current cost of COPD requires a repeat of the surveys undertaken previously with similar methodology but will depend on reliable prevalence estimates. Thus, this brief economic statement can only arrive at a cost estimate for COPD in 2000-01 by extrapolating the 1993-94 AIHW cost estimates of the health sectors of COPD taking into account current available statistics.

Direct cost estimates for COPD for 2000-01 and 1993-94 are provided in Table 1. The hospital cost for COPD (E65A and E65B) for 2000-01 was obtained from the AIHW National Hospital Morbidity Database and assumed to represent 37.3% direct costs for COPD as estimated in 1993-94 by AIHW. The costs for the other health sectors were then calculated assuming pharmaceuticals represented 22%, medical costs 20.3% and other costs 20.3% of total direct costs as estimated in 1993-94.

Table 2. Estimated direct costs of COPD

Costs	COPD 1993-94	COPD 2000-01
	AIHW data	(AIHW data)
	(\$A million)	(\$A million)
Hospital	112	188
Medical	61	102
Pharmaceutical	66	111
(prescribed and over the counter)		
Other	61	102
TOTAL	300	503*

*The estimated total direct cost of COPD of \$503 million does not include the direct costs of related diseases and conditions associated with COPD. It therefore represents an underestimate of the true health system impact of the disease.

Indirect Costs

Indirect costs mainly focus on lost production caused by the disease or premature death and borne by the individual, family, society or employer. They can also cover costs incurred outside of the health system. Indirect costs may include loss of earnings to the patient through

early retirement or premature death, loss of potential tax revenue for the government, loss of earnings and productivity due to absenteeism, social welfare payments to the patient, the cost and emotional impact on carers, the cost of equipment/devices, modifications to housing, and the cost to the community including volunteer organisations and alternative care facilities (75). They may also contain a value that society places on human life and the relief of pain and suffering. Their inclusion in estimating the cost of illness remains controversial and only rough estimates are usually possible.

It is very difficult to estimate indirect costs for COPD. COPD patients experience progressive disability associated with the decline in lung function. The majority of people are incapable of productive work within a few years of diagnosis of COPD. They can also have a marked reduction in quality of life (17). COPD patients and their carers may experience considerable depression and anxiety in relation to the illness and its associated disabilities which are difficult to quantify (81).

Total Cost

An estimate from the US attributed 56% of the total cost burden of COPD to direct costs and 44% to indirect costs (82). Another estimate attributed 61.5% cost of COPD to direct costs and 38.5% cost to indirect costs.(83) Applying these estimates to COPD would give an estimated indirect cost for COPD in Australia during 2000-01 ranging from \$315-\$395 million.

Combining the estimates for direct and indirect costs provides a total cost estimate for COPD in Australia in 2000-01 ranging from \$818 to \$898 million dollars (Table 2).

Table 3. Total cost estimate for COPD 2000-01

COPD direct cost (\$ Million)	COPD Estimated direct cost as % Total cost	COPD Estimated indirect cost (\$ Million)	COPD Estimated total cost (\$ Million)
503	56	395	898
503	61.5	315	818

In 1998 the Australian Lung Foundation employed the method of Hensley and Saunders(54) estimated the total direct and indirect cost of COPD in Australia to be approximately \$800 million(81). This estimate is similar to the estimates in Table 3 above.

Home Oxygen Therapy

Home oxygen or long term oxygen therapy was introduced to Australia during the 1970's, not long after Petty and Flenley started using this intervention in the United States and United Kingdom (84). The mode of oxygen supply at that time was by large "E" size cylinders which were large, heavy and, to many patients, unsightly objects. The Flinders Medical Centre (FMC), a 425-bed tertiary referral public hospital was commissioned in 1976 in southern Adelaide and almost immediately became involved in providing home oxygen therapy to patients assessed by the Respiratory Unit as requiring this therapy. At that time the method of delivery of oxygen was in the form of large "E" size oxygen cylinders. These cylinders required frequent replacement.

I travelled overseas in 1976, 1978 and 1980 to meet the key experts in home oxygen therapy including Professors Tom Petty, Nick Anthonisen, David Flenley and Peter Howard, all of whom at that time were involved in randomised controlled trials of oxygen therapy (1, 2). I also visited several oxygen concentrator and oxygen supply companies in the US and UK during this visits and became convinced that the concentrator provided a more economical and efficient method of oxygen delivery.

In 1980 an oxygen concentrator was imported to Australia by the spouse of one of our patients suffering from emphysema who was receiving long term oxygen via cylinders. In 1982, two oxygen concentrators were donated to FMC by two different manufacturers (DeVilbis and Marx) based in the USA. These devices were trialled on a male and female patient receiving LTOT in the Adelaide metropolitan area. The initial acceptance of this device by these patients led to a submission to the South Australian Department of Health for a grant to purchase 40 units. Funds were finally obtained for the purchase of 34 concentrators by FMC and these replaced large cylinders for the existing patients on LTOT. At the same time an Australian who

had worked as a Respiratory Therapist in the USA imported 15 oxygen concentrators into Australia and also I was able to bring back to Australia 2 concentrators for evaluation at the conclusion of my overseas visit in 1980.

Up to this point in time the only published guidelines or recommendations came from the American College of Chest Physicians in 1973 (3) and the American Thoracic Society in 1977 (4). In 1982 the staff of the Respiratory Unit, FMC held a workshop where it was agreed that patients would be assessed for home oxygen therapy using the 1977 American Thoracic Society Guideline.'

Ann Woolcock presented a paper during a symposium entitled "Long Term Oxygen Therapy: A World View" held in Toronto, Canada where she estimated that at that time 2,100 patients were receiving oxygen in New South Wales for an average of 1 hour per day. She further reported that the use of cylinders ranged from 1 cylinder a year to 14 cylinders per week. Physicians were reported to have been conservative in their approach to oxygen therapy and that only 50 people were on long term oxygen therapy in New South Wales. Woolcock mentioned that oxygen concentrators were available but provided no specific details of their use in Australia(5).

The first Australian guideline for the provision of domiciliary long-term oxygen therapy appeared in 1985. This guideline was developed at the request of the Thoracic Society of Australia and New Zealand (6). In the same year I published a study on the provision of oxygen therapy via an oxygen concentrator based on our initial experiences with this technology (7). In the following year I published a paper documenting the analysis of the costs for providing home oxygen therapy. I also reported how Cost-Centre Management led to the introduction of practical measures for improved clinical decision-making and improved expenditure control resulting in substantial cost savings(8). McKeon et al reported the

rationalisation of the supply of home oxygen in the Hunter region of New South Wales (9).

This paper also reported the one to five year survival rates for their patients (n=111) that were $94 \pm 2.6\%$ (mean \pm SEM) at 1 year, $80 \pm 4.4\%$ at 2 years, $36 \pm 5.4\%$ at 5 years. At that time only between 5 and 12% of patients received oxygen via an oxygen concentrator.

In general the taking of medication is a simple behaviour that must occur only a few times a day at most. It is a behaviour that can, in most cases, be performed in private mostly without an audience. Whilst deciding whether or not to take a medication may be complex and multifaceted process, the actual act of taking the medication is not. Regular medication taking requires an alteration to the daily ritual and perhaps some degree of organisational skills but not much else. However, adherence is only about 50% for many conditions. Oxygen is a different matter.

At best, oxygen therapy is cumbersome with the patient 'tethered' to the oxygen source that, in the past, limited the movement of the patient due to the size and weight of the oxygen cylinders. Other issues such as "embarrassment" or "self-consciousness" at being seen to be on oxygen therapy in public may influence its use by patients. Oxygen concentrators provided a partial answer to these problems.

The introduction of the oxygen concentrator led to ongoing evaluation of the impact on patient care and acceptance of the intervention and whether the expected outcomes, increased survival and quality of life, were achieved (10). In 1991 I published South Australian data on survival for patients receiving home oxygen therapy. The results of this study indicated that the mortality rate for COPD at 1 year was twice the rate reported by the Medical Research Council Working Party and the Nocturnal Oxygen Therapy multicenter trials. Median survival at for our COPD patients at this time was 18 months (95% Confidence Interval 13 – 28 months) for males and 46 months (95% C.I. = 30 –51 months) for females (14). The baseline

physiological parameters for our patients were similar to the patients in the MRC and NOTT benchmark studies. I was later able to show that survival of our long term oxygen patients was no better than the control group of the original MRC study (11-13). The second significant observation was that females survived longer than males (14). Possible hypotheses for this difference include that our patients were different to those studied in the RCT's since that there were no inclusion or exclusion criteria in our group in terms of co-morbidities, age differences and whether the use of liquid oxygen therapy as opposed to the oxygen concentrator provided some survival advantage. The survival of twenty-two of our COPD patients receiving their therapy via liquid oxygen was 52.11 months and 27.75 for n=698 COPD patients $p=0.004$. (Unpublished data).

In 1992 a further paper was published reporting that in spite of strict prescription criteria and the introduction of oxygen concentrators as a cost-saving new technology, the budget for this intervention remained under pressure. This was largely due to a rapidly increasing demand from eligible patients (10). A further analysis of the longitudinal data resulted in a report of an association between home oxygen therapy with a reduction in respiratory admissions and bed days (15).

At this time there was a relative paucity of information about the trends of mortality in COPD in Australia. To further understand the burden of disease (COPD) and changing trends in mortality over time a research project was undertaken. It indicated that the mortality of females from COPD increased whilst it was decreasing in males (16)

Oxygen cannot be used inconspicuously. It is always a conscious and very public event that impacts on the patient's quality of life. Unlike a tablet or injectable medication, being tethered to the equipment involved in using supplemental oxygen is a constant reminder, to the patient

and to others, of the illness that necessitates its use. Oxygen therapy, either physically or aesthetically, will in some way alter every activity in which the patient engages while using it.

The relatively poor survival outcomes for our home oxygen patients prompted further attempts to understand the costs and benefits in terms of quality of life and the evaluation of two generic health-related quality of life questionnaires available at that time in 1996. The results of the study suggested that the sole use of the SF-36 as a health outcome measure in COPD patients might fail to provide information about the mental domains of their quality of life. Decreased cognitive function, anxiety and depression have been reported in COPD patients (17).

A series of papers describing the observations made on Australian home oxygen patients were published between 1996 and 2000 (11, 18, 19, 20). Further attempts to rationally allocate resources in the management of COPD were reported in 1999 using Program Budgeting and marginal analysis (21). In the year 2000 we undertook a systematic Cochrane Review of the five randomized controlled trials of the use of home or long term oxygen therapy in COPD demonstrating that this intervention improved survival in a selected group of hypoxaemic COPD patients. However, this intervention does not appear to provide any benefit for patients with moderate hypoxaemia or nocturnal desaturation (20). This review has been translated into several languages and is cited as the basis of many more recent guidelines concerning long-term oxygen therapy.

More recently, a NH&MRC funded report was published reviewing the impact of evidence based clinical practice in relation to long term oxygen therapy. In this report we explored to relationship between the evidence and the observed outcomes in terms of both survival and quality of life (13, 23, 24). Finally, we conducted a study of the relative survival of our patients

compared to those patients with similar characteristics in France. We demonstrated that our patients relative survival was less than their French counterparts (25).

My publications alerted health professionals to the costs involved in the delivery of long term home oxygen therapy. I went on to suggest an economical new technology as a solution to this problem and one that has changed standard practice in Australia. I have also provided detailed information on the impact of the intervention on survival, quality of life and other health outcomes. My publications were the first to report quality of life outcomes for these Australian patients.

CHAPTER 2

Literature Review

Historical Aspects of Oxygen Therapy

Oxygen is the most essential element of life. Man's need to breathe posed a challenge to the early Chinese, Indian and Egyptian medical systems more than 4,000 years ago. (85) At that time some of these cultures believed that a vital substance, without which life would come to a stop, was taken up in the lungs. This is a remarkable insight during that era into the physiology of respiration.

The Chinese probably produced oxygen more than 2,000 years ago by heating nitre to a high temperature. However, they failed to identify the products of this combustion as a new gas. In 1678 Ole Borch (1626-1690) heated nitre and discovered that the gas produced nourished fire. Since there were no methods available at that time to collect this gas the observation was not pursued. Georg Ernst Stahl (1660-1734) advanced the "phlogiston theory" in 1697. This theory claimed that phlogiston existed in all substances that were combustible; this substance was so finely dispersed in the atmosphere that it could not be detected by the senses. At the same time as these important discoveries Richard Lower (1641-1691) demonstrated that the lungs were the site where arterialization of the blood occurred. John Mayow (1640-1679) believed that air contained a substance (spiritus nitro-aereus) that sustained a burning candle and was inhaled during respiration. Despite the fundamental role that oxygen plays in life, this theory prevailed until Lavoisier (1743-1794) discovered the central role of oxygen in the process of combustion (85).

In most texts the discovery of oxygen is attributed to Joseph Priestley (1733-1804) in August 1774. Priestley published his findings in 1775. However, the Swedish apothecary Karl Scheele also discovered oxygen independently in 1772 but did not publish his results until 1777. It was

likely that Priestley was the first person recorded to inhale a gas mixture with a greater than normal ambient concentration of oxygen. His description of the experience is quoted below.

"My reader will not wonder, that, after having ascertained[sic] the superia [sic] goodness of dephlogisticated air by mice living in it, and the other tests above mentioned, I should have the curiosity to taste it myself. I have gratified that curiosity, by breathing it, drawing it through a glass-syphon, and by this means, I reduced a large jar full of it to the standard of common air. The feeding of it to my lungs was not sensibly different from that of common air; but I fancied that my breast felt peculiarly light and easy for some time afterwards. Who can tell but that, in time, this pure air may become a fashionable article in luxury. Hitherto only two mice and myself have had the privilege of breathing it."

Joseph Priestley. Experiments and Observations on Different Kinds of Air. Vol. 2. London: J Johnson, 1775. Reprinted in: Comroe, JH. (ed). Pulmonary and Respiratory Physiology. Part 1. (Benchmark Papers in Human Physiology /5) Pennsylvania: Dowden, Hutchinson & Ross, 1976

Lavoisier named Priestley's gas "oxygen" because of its tendency to create acids when combined with other elements (86). Physicians were quick to attribute the role of lack of this gas in the aetiology of many diseases.

The first use of oxygen as a therapy is attributed to Caillens in 1783. One year later Jurine, in Switzerland, published an essay on the use of daily inhalations of oxygen for the treatment of phthisis in a young woman. In France, Chaptal reported the use of oxygen in two more case of phthisis where only one patient benefited in 1789. Ten years later in 1799 the *Bristol Gazette and Public Advertiser* announced the Pneumatic Institution, founded by Thomas Beddoes

(1760-1808), for inhalation gas therapy. During the relatively short life of the institute Beddoes employed Humphrey Davy (1778-1829) and James Watt (1736-1819) to manufacture the oxygen. The therapeutic administration of oxygen was based on the generally incorrect assumption that some diseases would respond to either higher or lower oxygen concentrations (87). At that time Beddoes considered that pulmonary tuberculosis was considered a disease that required treatment with low concentrations of oxygen. The institute closed in 1802 after no real clinical benefit was obtained from their interventions.

Between 1800 and 1857 there were a series of reports of the benefits of oxygen therapy in individual patients suffering from phthisis in the United Kingdom and the United States. The need for oxygen in the human body was definitively demonstrated in a series of balloon ascents in the late 19th century. The first attempt by Galshier and Coxwell reached the height of 29,000 feet where one of the party lost consciousness. The French physiologist Paul Bert, published a book in 1878 describing that the principle effect of altitude on humans was to lower of the partial pressure of oxygen in the human body. He also suggested that the physical and mental dysfunction at high altitude was a result of the lack of oxygen to the vital organs (86).

In 1857, Dr S.B. Birch published papers in *The Lancet* (88) and the *British Medical Journal* (89) reporting the use of oxygen in low doses in seven cases suffering a variety of complaints including diabetes mellitus, end-stage phthisis pulmonalis, paraplegia, menopause and loss of vision. Birch also recommended that "extended and fair trials" be undertaken before oxygen was admitted into the list of the then current therapeutic agents.

The first publication in the USA concerning oxygen therapy has been attributed to Samuel Wallian in the *Chicago Medical Journal* in 1869 (88). A year later Andrew H Smith MD of New York won the "prize essay of the Alumni Association of the College of Physicians and

Surgeons, N.Y.” with a paper titled ‘Oxygen gas as a remedy in disease’. He recommended a treatment regime consisting of 2 litres per minute flow rate for 8 minutes morning and evening. In the late 19th century it was reported that one of the barriers to the use of oxygen was its high cost of production. Even at this early period the device used for the production of oxygen was made available for hire at approximately £1.1.0 per month. This amount was equivalent to approximately two weeks pay for a labourer at that time. In current terms this monthly charge would be equivalent to half the capital cost of an oxygen concentrator.

It is interesting to note that William Osler, the famous clinician, only made brief mention of oxygen therapy in the first edition of his textbook ‘The Principles and Practice of Medicine’.(88) It would seem from statements about the treatment of pneumonia in the 3rd edition of his text that Osler did not use or recommend oxygen therapy for his patients. However, by the end of the 19th century despite of lingering doubts about oxygen's utility, possibly related to the relative impurity of the gas manufactured, this intervention became accepted by an increasing number of medical practitioners.

In the early 1900's there were numerous papers published about intra-abdominal, intravenous, rectal and subcutaneous administration of oxygen.(88). The modern era of oxygen therapy commenced around the time of World War I when J.S. Haldane (1860-1936) published his experiences in treating war gas injuries. Haldane and Barcroft commented on the physiology of hypoxaemia in a discussion on the therapeutic uses of oxygen at the Royal Society of Medicine, London in 1920. It was these comments which led Barcroft to lay down the modern concepts for the use of oxygen as a general rather than a specific remedy.(90).

In 1921 that Metzler further developed the work of Meakins and demonstrated the efficacy of oxygen therapy in pneumonia, asthma, chronic bronchitis and emphysema as well in the treatment of the effects of gassing experienced by the soldiers during the First World War. In

the United States the focus was on the treatment of pneumonia and Leigh reported that Binger demonstrated that the oxygen saturation levels obtained in the patients blood when they were administered 40% FiO₂ were of significant prognostic value.(90).

The frequency of administration of a drug is based on elementary laws of therapeutics where the frequency should be associated with optimal blood levels of the substance. This implies that the half-life of oxygen in the blood is known. In the early decades of oxygen use it was prescribed in intermittent dosage (90). The half-life of oxygen appears to be in the order of 10 – 15 minutes since PaO₂ levels fall to baseline values approximately 20 minutes after the cessation of oxygen therapy. The rate of fall seems to depend on the oxygen consumption of the individual and the degree of respiratory pathophysiology. However, after more than 200 years of in many cases misguided intermittent use, physicians of the 21st century continue to prescribe, and, patients continue to use oxygen in intermittent doses. This is despite evidence supporting the use of continuous oxygen therapy being available since the first decade of the 20th century.

It is reputed that Haldane made the apocryphal statement: "Intermittent oxygen therapy is like bringing a drowning man to the surface of the water – occasionally" and Moran Campbell added "I think that it is like pushing him down between times" (91). These statements were preceded in 1962 by the discovery that intermittent oxygen supplementation was invariably followed by arterial hypoxaemia to a greater degree than the levels observed pre oxygen therapy (90). Haldane also is reported to have said that "hypoxia not only stops the machine but wrecks the machinery" (92). Six years later Petty and Finigan demonstrated the benefits of the treatment of chronic hypoxaemia with the reversal of pulmonary hypertension and secondary polycythemia as well as improved renal plasma flow and a reduction in infections (93).

Both Haldane's and Barcroft's understanding of oxygen therapy was underpinned by their major involvement in firstly, the development of manometric methods of gas analysis for blood and gas mixtures and secondly, the many investigations carried out in to the oxyhaemoglobin dissociation curve (85). It took Leland Clark's development of the first polarographic oxygen electrode in the early 1950's to provide a relatively easy method of evaluating the impact of oxygen therapy by the measurement of arterial oxygen tension.

Oxygen was prescribed as a flow rate in the early days of modern oxygen therapy. This practice continues to this day. Haldane in fact advocated that "the minimum quantity of oxygen which will remove the cyanosis should be carefully ascertained by observation of the patient, and the governor adjusted to give this minimum quantity which is likely to be anything from 1 to 3 litres per minute" (90).

In 1922, the American Physician Alvin Barach stated that the role of oxygen in medical therapy was still uncertain. He remarked that prior to World War I (WWI) there was an "indifference to its use" and "scepticism concerning its (oxygen) value (94). Barach believed that this situation had arisen due to the lack of an "ideal" method of administration. At that time oxygen was delivered to the patient via a rubber tube from the cylinder and funnel to be held close to the face. Metzler claimed that this method only raised the inspired oxygen concentration by approximately 2% (95).

During WWI an apparatus developed by Haldane was found to be frequently "life-saving" in treating acute cases of gas, predominantly phosgene poisoning (96). In the period immediately after WWI, Barcroft in Cambridge and Shufflebotham and Sowry in Stoke had success in treating chronic cases of gas poisoning (94). Both groups showed that oxygen therapy not only improved cardiac function in terms of reduced heart rate but also reversed polycythemia.

Shufflebotham and Sowry used an oxygen chamber to treat patients with pneumonia with some success. However, they found that in the case of pernicious anaemia the initial improvements noted whilst the patient received oxygen were lost once they exited the chamber. We now understand this to be due to the lack of haemoglobin to transport oxygen or the positive effect due to dissolved oxygen in the absence of cardiopulmonary disease.

At this time it was observed that the improvements in oxygen saturation, during oxygen therapy, were coupled with an improvement in the patient's clinical status. It was also noted that prolonged use of oxygen in patients with clinical pulmonary oedema was life saving. These and other observations led Barach to write, "It would seem theoretically desirable to keep the patient free from cyanosis as many hours of the twenty-four as possible". This is possibly the first reference to continuous oxygen therapy. At the same time he noted that "Subjective dyspnoea does not seem to be due to oxygen want, nor is it relieved by the inhalation of oxygen" (94).. The debate about this latter relationship continues to-day (97).

Barach summarised the necessary conditions for oxygen therapy as:

- (1) It is necessary to provide an effective concentration.
- (2) Oxygen therapy apparatus and administration of oxygen should produce no discomfort to the patient.
- (3) The economy (cost) of the method has to be considered.

Barach also called for a thorough clinical trial (in pneumonia) and discussants of the paper added a call for statistical evidence. It took almost 60 years for these calls to be answered with the publication of two randomized controlled trials.

Comroe and Drips (29) outlined the rational, physiological basis for oxygen therapy and also raised the issue of possible harms from this therapy in 1950. Cotes and Gilson (98) described the benefits of oxygen therapy during exercise using a portable apparatus and in 1959 Barach (99) applying the physiological principles outlined by Comroe and Drips reported on "ambulatory oxygen therapy: oxygen therapy at home and out-of-doors" using cylinders imported from England.

What followed was a debate about the relative merits of 'controlled' and 'uncontrolled' oxygen therapy. Controlled oxygen therapy appeared after the introduction of Ventimasks by Moran Campbell (91, 100, 101). Leigh remarked that this referred to "the administration of known doses of oxygen generally 24,28 and 35%'.(90). This term has been used in association with a variety of other masks where the concentration delivered to the lung is generally not known. In North America the effective delivery of oxygen to the patient was achieved in the 1960's with the development of a plastic double-pronged nasal cannula (86).

In retrospect there appeared to be two major limitations in the use of oxygen during the early 20th century. The first was associated with problems of delivering the gas to the patient. The most common method was through a funnel that was placed near the mouth. This method failed to significantly raise the concentration of oxygen in inspired air to make a clinically significant difference. Secondly, the method of producing oxygen only allowed for use for relatively short periods of time. At this time the production of oxygen was achieved by heating various oxides and other chemicals that only resulted in small volumes of gas (102).

The one thing lacking was scientific evidence on the efficacy of long-term oxygen therapy. The Denver Group including Levine and Petty published a paper in 1967 showing that oxygen therapy for a period of one month decreased pulmonary artery pressures and reduced the red cell mass. They also demonstrated an increase in the patient's activity levels and feeling of

well-being in patients with emphysema (103). The Denver Group then initiated a small long-term oxygen program involving approximately 30 patients. This program was hampered by debates on who should be responsible for the cost of providing this therapy and was threatened again when the major supplier announced that it was getting out of the medical oxygen business. This scenario was repeated when a home oxygen program was being established in the southern region of Adelaide in the 1970's (8, 10, 104).

Long Term Oxygen Therapy

Although the evidence demonstrating the benefits of long-term oxygen therapy began to accumulate, a consensus was reached in the 1970's that a large prospective clinical trial was needed (86). In 1980-81, two randomised controlled trials (RCTs), conducted respectively by the United States Nocturnal Oxygen Therapy Trial Group (NOTT) (1) and the British Medical Research Council (MRC) (2) reported an increased survival in COPD patients prescribed a continuous (ideally 24 hours every day) inspiration of a moderate flow of oxygen. The NOTT study also commented on relatively small improvements in neuropsychological function and quality of life, although these could not be ascribed with certainty to the oxygen therapy. Since the RCT findings were in accord with physiological evidence and clinical acumen, long-term home or domiciliary oxygen therapy (LTOT) has become a major form of treatment for COPD. A substantial new industry for the supply of this therapy has developed both internationally and in Australia.

It is of interest that the MRC study had relatively few subjects and that there appeared to be no survival advantage for males until after 500 days of therapy. The Relative Risk Reduction (RRR) for males is approximately 58% whilst the Absolute Risk Reduction (ARR) in mortality is 17% and the Number Needed to Treat (NNT) = 5.9. However, the power of the study to detect a real difference is relatively low at approximately 40%. Females appeared to have a significantly better survival. However, low numbers of females in both the control (n=12) and

the intervention (n=9) arms of this study further weakens the external validity of results. The RRR for females was approximately 84% and the ARR 30.8% and NNT = 3.2. Again the power of the study to detect a difference in females was low lying between 43 and 53%. It must be remembered that at the time of the NOTT and MRC studies COPD was considered to be a predominantly a male disease. My study reported in Chapter 5 was amongst the first prospective studies that involved almost equal number of males (n= 78) and females (n=64) (14).

In view of the late survival benefit observed in the NOTT and MRC studies the present climate of opinion would negate on ethical grounds the possibility of any further RCTs of LTOT for COPD. However, the two RCTs did not settle all the important issues, including: the optimal selection criteria for prescribing LTOT, the effect on health-related quality of life (HR-QoL) over time; possible reasons for the survival advantage for females compared to males in the MRC study; and the influence of concomitant disease.

The MRC trial did not incorporate a placebo (medical air was rejected on the grounds of cost). The survival curves for the males in the treated and untreated arms did not diverge until 500 days after admission to the trial. The NOTT study essentially demonstrated a dose-response effect for hours of oxygen per day, but did not incorporate an untreated control group. In both trials, it was conceivable that differences in smoking cessation might have influenced the results. Data from European studies has been unable to replicate the survival rates achieved by the NOTT/MRC studies (105, 106). A frequently held clinical belief exists that LTOT will give COPD patients an additional five years of life. In a retrospective study that I conducted in 1991 at the Respiratory Unit at Flinders Medical Centre (FMC), I was able to show that in routine clinical management of patients with severe COPD, survival on LTOT was significantly shorter than that documented in the original trials. It but was similar, however, to the results

reported by Strom and Dubois et al. (14, 107, 108) and almost twice as long as those reported from the Danish Oxygen Register (109). These observations should be taken into consideration in writing the oxygen therapy guidelines

The guidelines recommend the use of LTOT for respiratory failure, i.e. end-stage disease. I therefore hypothesized that part of this failure to achieve similar survival results may be due to the frequency and severity of concomitant disease present and/or the advanced age of these patients. Most COPD patients at FMC on LTOT are elderly and have compromised function across several organ systems.

Neither the NOTT nor the MRC trials found a statistically significant difference in hospitalizations. However, in the MRC trial at least, clinical supervision was acknowledged to be much more frequent than in routine practice, so that hospital admission was arranged very early in any exacerbation. Subsequently, substantial potential savings from averted hospitalizations after the prescription of LTOT have been demonstrated.(110) I was able to demonstrate similar potential savings at FMC (15). However, the realization of the savings as actual reductions in hospital expenditure is offset by admissions from the waiting lists of patients for other medical or surgical conditions. The current guidelines of the Thoracic Society of Australia and New Zealand (TSANZ)(111) and the South Australian Department of Human Services (112) for the prescription of LTOT for patients with lung disease are based on the evidence obtained from the NOTT and MRC RCTs.

Previous studies have shown poor prescribing habits for LTOT in the United Kingdom.(113, 114). Prescribing habits amongst Australian physicians have not been formally investigated. In addition, it is unknown how often Respiratory Physicians delegate the prescription of LTOT to more junior medical staff or how frequently general practitioners prescribe LTOT without formal assessment. In times of great financial pressure on health care institutions there is an

imperative to reduce length of in-patient stay (LOS). Clinically unstable patients may be discharged from hospital earlier than would otherwise be appropriate by being prescribed LTOT (without formal assessment) to free up hospital beds. The prescription of LTOT in these situations may not comply with TSANZ guidelines. It is unknown whether the prescription of LTOT outside the guidelines is valid and produces clinical benefits.

Health-related quality of life has become increasingly important as an outcome measure for health interventions. There is little documentary evidence of the impact of LTOT on HR-QoL. The original NOTT randomized controlled trial investigated the effect of oxygen therapy on HR-QoL. The NOTT study subjects underwent baseline neurological testing and assessments were made of emotional status and general quality of life using the Minnesota Multiphasic Personality Inventory (MMPI), Profile of Mood States (POMS), and the Sickness Impact Profile (SIP). None of these measures were designed specifically for patients with COPD. However, some patients with COPD were included in the subjects used to validate these generic tools. In the NOTT study some measures of neuropsychiatric function were shown to improve. However, no measures of quality of life improved after six months of oxygen therapy (115). These results seem to contradict each other. If oxygen provides so many benefits both in terms of mortality and physiologically in patients with COPD, why is there not a more measurable effect on HR-QoL? (86)

The majority of the more recent reports of HR-QoL in COPD have been confined to mild to moderate disease states (116). Patients with COPD tend to be withdrawn and avoid social interaction that leads them to become isolated, lonely. Approximately 40% of patients admitted to hospital with COPD are assessed as being anxious and depressed. It has been postulated that COPD patients develop a unique psychology that results from attempts to avoid the sensation of dyspnoea (86). Neff and Petty introduced the term "respiratory panic" to describe

the emotions felt by COPD patients when they experienced exertional dyspnoea (117). Long-term oxygen therapy could be expected to at least ameliorate these symptoms that are associated with COPD and have a positive impact on the patient's HR-QoL. There is no evidence that this in fact occurs.(86)

The patterns of response to COPD and in particular hypoxaemia are acquired gradually over a relatively long period of time. The impact of LTOT in the short term is unlikely to have a measurable positive on HR-QoL. Dyspnoea is also a complex phenomenon of which hypoxaemia is but one component of this symptom (118). It is therefore likely that correction of hypoxaemia alone would not completely relieve the symptoms of dyspnoea. Another possible mechanism might relate to the oxygen therapy itself, resulting in negative impact on HR-QoL that blunts or negates the beneficial physiological effects of oxygen.

Unfortunately, most equipment used by patients prescribed LTOT may restrict their mobility, thereby reducing any beneficial impact this therapy may have on their quality of life. Oxygen that is administered via the nares often attenuates the sense of smell and taste (119). There are also many other factors that may impact on the HR-QoL of COPD patients. They tend to be older, they may live alone having experienced the loss of spouse, they may have had to retire prematurely or, as shown in the FMC COPD patients, have multiple co-morbidities. As with most medical therapies compliance with LTOT has been reported to relatively poor. Phillips et al suggested that estimates of oxygen use were often 30% greater than the real use (120).

Oxygen therapy has a long history. In the 18th century oxygen use was largely empirical and based on the notion that since oxygen is essential to life. The administration of more of it must be beneficial to health. Athletes and the advent of "oxygen bars" in department stores and beauty clinics in part retain this notion to day with the use of oxygen. There has been a large

amount of evidence accumulated over the past several decades documenting the efficacy of LTOT in treating oxygen-deficient states. Despite evidence existing of physiological efficacy prior to my studies reported in 1991(14), there had been only one other study which briefly documented the impact of LTOT on the survival of Australian COPD patients (9).

The MRC study provided oxygen treatment for at least 15 hours a day to 33 males and 9 women who had a PaO₂ between 40 and 60 mm Hg. A total of 33 men and 12 women formed the control group (2). In the NOTT study 809 patients were excluded from the original cohort of 1,043 patients screened for the study. One hundred and two patients were randomly allocated nocturnal oxygen and 101 allocated continuous oxygen therapy (1).

In the study by Fletcher et al (121) only 16 of the 38 COPD patients with nocturnal desaturation were randomised to either sham treatment (N= 9) or oxygen via a concentrator (N= 7). Gorecka et al's study of moderately hypoxaemic COPD patients (N=135) randomised almost equal numbers to the treatment (N = 68) and control (n = 67) arms of the study. Chaouat et al's study (122) originally randomised 76 to nocturnal oxygen (n = 41) and control group (n=35). Only 24 treated and 22 control patients were available for follow-up at 2 years.

In my systematic review I highlighted several problems with the patient selection and study design (20). Only one of the included studies was double-blinded due to the inability to practically blind the patient and health care provider to liquid oxygen therapy. The treatment regime for the control groups in the reported studies varied from none for the Górecka's study (105), nocturnal oxygen therapy for the NOTT study to a sham treatment through a disabled oxygen concentrator, which delivered the equivalent to 25% oxygen therapy in the Fletcher study (121). In this latter study, this level of oxygen therapy for the control subjects may have confounded the results because this higher than ambient inspired oxygen concentration may

have been reflected in the PaO₂ in this group. The control group in the MRC study did not receive a sham treatment regime.

In the NOTT study, the numbers of patients receiving the different modes of oxygen delivery were not reported. In the MRC study there were some basic differences between treated and control groups at baseline. Females in the treated group appeared to have more compromised lung function than those of the control group whilst the reverse appeared to be apparent for the male patient groups. The mean number of hospitalizations and hospitalized days in the Fletcher study could not be included in the Cochrane Review, as standard deviations were not given. The Górecka study (105) reported differences in studied variables by survivors and non-survivors.

No data was reported in the two major studies (NOTT and MRC) about the effects of continuation or cessation of smoking or indeed if smoking status affected the outcomes. The mean PaCO₂ at baseline was higher in the MRC study than in the NOTT study. This did not appear to influence the results. Other known prognostic indicators such as body mass index (BMI) were not discussed in either of the studies. The lack of frequency of exacerbations' data is also a further limiting factor in interpreting the results. There have been other RCT's in recent years that are included and discussed in detail in my Cochrane Review (See Chapter 10 of this thesis).

Quality of Life

The term "quality of life" has many meanings that reflect the particular knowledge, experiences, and values of each individual. These relationships and the fact that an individual's perception of 'quality of life' changes over time have been known for almost 2500 years. As the Athenian philosopher Aristotle wrote:

"When it comes to saying in what happiness consists, opinions differ, and the account given by the generality of mankind is not at all like that of the wise. The former take it to be something obvious and familiar, like pleasure or money or eminence, and there are various other views, and often the same person actually changes his opinion. When he falls ill, he says it is his health, and when he is hard up he says it is money" (123).

Given the age of most patients receiving LTOT, the majority receiving pensions, it would seem that "happiness" or quality life would be affected by both their physical and mental health and economic circumstances. More importantly it has also well recognized that medical interventions can be both enabling and disabling. It is possible that the gains and benefits that LTOT provides to the patient may also create new problems or difficulties, for example the "tethering" of the patient to the cylinder or oxygen concentrator. The logistics of ensuring a continuous supply of oxygen can also be daunting for some patients. Limited mobility may further be exacerbated because of the design of equipment in spite of supplemental oxygen providing benefit and increased exercise tolerance (124, 125)

The concept of quality of life is value laden. Dubos argued that "quality of life involves highly subjective value judgments" which also can be described as "profound satisfactions from the activities of daily life" (126). The early work of Dudley investigating the psychosocial concomitants in COPD during the late 1960's and 1970's initiated the interest in psychosocial issues and quality of life(127-130). Fishman and Petty (131) included psychological testing in their evaluation of comprehensive COPD care about the time LTOT was being introduced in North America. In 1981 Brown et al (132), using measures of life satisfaction, reported that

COPD patients were significantly less satisfied, less socially active and more disabled and perceived that their health was poorer than patients with coronary artery disease.

The original NOTT randomized control trial of LTOT included 3 measures of quality of life, the MMPI (a 566 question inventory measuring 10 dimensions of emotional and personality disturbance) the Profile of Mood States (POMS) and the Sickness Impact Profile (SIP).

McSweeney et al reported that the quality of life of 203 COPD patients who were enrolled in this study was diminished in the domains of emotional functioning, social-role functioning, activities of daily living, and recreational pastimes (115). He argued that these observations had major implications for the management of COPD and for the evaluation of medical treatments. Prigatano et al (133) found similar results in mildly hypoxaemic patients to Mc Sweeney findings in severely hypoxaemic patients. However, the degree of impairment was less in Prigatano et al's subjects (133).

At least one study has reported some positive effects of COPD in relation to care of grandchildren and marriage (134). Women with COPD were found to have lower perceived health status, more subjective stress and less life satisfaction than controls (135). This later study is one of the few reporting on the effects of COPD on women. The majority of studies reported in the literature have larger number of male than female patients with COPD. This led to the early belief that it was predominantly a man's disease probably influenced by the pattern of tobacco use in the early and mid-20th century.

Many COPD patients may use a psychological defence mechanism that may include denial and repression to reduce the impact of emotional change on their failing respiratory system.

The link between COPD and panic attacks, anxiety and depression have previously been described in a group of South Australian out-patients (136) A more recent study undertaken in

Switzerland found that 21% of patients receiving LTOT suffered from anxiety and 27% from depression (137).

The ultimate purpose of all health interventions is not only to save lives but also to enhance the quality of life. Extending the length of life is not a sufficient goal when dealing with a chronic disease such as COPD. This is particularly so when the extended life is deprived of basic functions or if it is qualitatively less than human. Systems theory and clinical experience both tell us that you simply cannot fix one aspect of the disease (138). LTOT may affect many aspects of the underlying lung disease such as relieving hypoxia causing shifts in ventilation/perfusion ratios, vasodilatation and reduction in pulmonary hypertension. However, it also has an impact on the biopsychosocial aspects of the patients' life, for example, activities of daily living, on the family or caregiver and immediate social community.

Many, medical and surgical interventions both new and old, seem intuitively to be beneficial. In the past they often became part of 'usual' care even when there was a lack of convincing evidence of the benefits that they might provide the patient. However, the continuing escalation in health care costs demands that we evaluate any 'new' technology not just in the terms of their benefits, but also in terms of the cost/benefit ratio with that of the previously standard therapy for the same condition. The switch from providing LTOT via cylinders alone to an oxygen concentrator or liquid oxygen is one such example that is the focus of this thesis.

Williams, (125) in a sociological study in the United Kingdom in the early 1990's, found that 20% of patients using oxygen therapy reported that it markedly interfered with or restricted their lives, with an additional 19% moderately affected by this intervention. Based on these and other reports it was recognized that there was a need to gain a better understanding of the impact of LTOT on the HR-QoL in Australian COPD patients.

Over the last 15 years health-related quality of life has become increasingly important as an outcome measure for health interventions. The term "quality of life", as reported in the medical literature, does not appear to have a universally accepted meaning (139). However, items or domains such as physical, functional, emotional and mental well-being are generally assessed. The inclusion of non-health-related factors that may impinge on life circumstances remains controversial.

There has been considerable development of both generic and disease-specific instruments to measure HR-QoL since the late 1980's. My longitudinal study reported in this thesis used both generic and disease-specific instruments to measure prospectively the HR-QoL of Australian COPD patients using LTOT (11, 12, 17, 24). I had recognized that the majority of the COPD patients included in this study had numerous co-morbidities (140). It was felt that a disease specific measure of quality of life alone might miss measuring the impact of other co morbidities and factors on the patient's overall quality of life. This position was echoed in 2001 in a Scandinavian study that concluded that a comprehensive assessment of the effects of COPD requires instruments to elucidate disease specific effects but also the overall burden of the disease on day-to-day functional and emotional wellbeing (141).

At the commencement of the data collection, in the mid 1980's, the now most common generic HR-QoL tool - the Medical Outcomes Study Short Form 36 (SF-36) (142, 143) had not been fully developed and validated. Initially the Nottingham Health Profile was the questionnaire of choice and we added the validated SF-36 and used these two generic measures in parallel. The disease specific questionnaire used was Guyatt's Chronic Disease Questionnaire (144, 145). A UK based study found that Guyatt's CRQ performed slightly better than Paul Jones's St George Respiratory Questionnaire (146).

The Life Satisfaction Index was also used as it had been repeatedly observed that in spite of two patients having almost identical severity of disease one died early and the other would survive (147). I hypothesised that this may result from the patient's "will to live" or how satisfied he/she is with their life.

Quality of life measures

Nottingham Health Profile

The NHP is a generic measure of perceived health status and consists of two parts. Part 1, which was used in the reported studies, contains 38 items categorised into six areas: energy, pain, emotional reactions, sleep, social isolation and physical mobility (148). Part 2 of the NHP was not used, as it was considered irrelevant to the patients involved in this study due to their age and severe limitation of their daily activities. The Yes/No answers to the items of Part 1 were weighted according to the NHP manual. The weighted scores for each item of each area were then added together giving a range of possible scores for each area from 0 (best HR-QoL) to 100 (worst HR-QoL). The NHP has been criticised for failing to detect low levels of morbidity.(149) The NHP was my first choice as the generic questionnaire to be used in my studies. The Medical Outcomes Study Short Form Health Survey 36-item Questionnaire (SF-36) had not been developed for general use when I commenced measuring quality of life in LTOT patients.

Medical Outcomes Study Short-Form Health Survey 36-item Questionnaire

Originally developed by the Rand Corporation in the United States of America the SF-36 was constructed for use in the Medical Outcomes Study (142). This instrument has been extensively tested, found to be acceptable, and to fulfil stringent criteria of reliability and validity as a measure of health status in a wide variety of patients (150-152). It has also been found to be a useful and valid measure of general health status in patients with chronic lung disease (150). Five of the dimensions in the SF-36 are similar to those of the NHP. However, it is claimed that items in the SF-36, unlike the NHP, detect positive as well as negative states of health (151). The SF-36 has been advocated as a general health outcome measure in

Australia. Estimates of its parameters in the general population were obtained in the Australian Bureau of Statistics 1995 National Health Survey.

The SF-36 contains 36 items that measure health on eight multi-item scales plus an additional scale measuring change in respondents' health status over the past year. The eight health concepts covered are physical functioning, role functioning-physical, role functioning-emotional, social functioning, bodily pain, mental health, energy/vitality, and general health perceptions. The questionnaire was scored by recoding particular responses and then combining and transforming the items according to the SF-36 manual (143). The scale score generated for each health concept, ranged from 0 (worst health state) to 100 (best health state). An Anglicised version of the SF-36 developed and validated for use in the United Kingdom was chosen as the most appropriate version available for Australian conditions at the time this study began. The major changes to the original version consisted of replacing words such as 'blue' with 'low' and converting the distance walked from 'blocks' to 'yards'. Since then an Australian version of the SF-36 has been developed (152).

Chronic Respiratory Disease Questionnaire

The CRQ, a disease-specific HR-QoL measure for patients with COPD, consists of four dimensions: dyspnoea, fatigue, emotional function and mastery (the patient's feeling of control over their disease and its effects (144). Because the CRQ previously caused difficulties in comprehension amongst our COPD LTOT patients, it was modified as follows. Questions associated with the dyspnoea dimension were reduced by eliminating the free choice in questions one and three of the original questionnaire and presenting only a fixed list of items which make some people with lung problems feel short of breath, i.e., question two. Only items so identified were then used in question four. Additionally, question ten was reworded to eliminate a grammatical error in the original. Each question in the CRQ dimensions of fatigue,

emotional function and mastery was presented as a seven-point scale. Each dimension was scored as the sum of the scores for all questions within the dimension. In addition, a total score was obtained by adding together the scores of the individual dimensions. Higher scores represented better health. Guyatt considers a difference in score from baseline of 0.5 for an individual question to be clinically significant (152). Thus the clinically significant difference was considered to be a change of more than 3.5 for the emotional function score and more than 2.0 for the fatigue and mastery scores. The proportion of patients who were able to change their CRQ scores by more than the clinically significant difference for each dimension was calculated (152).

Life Satisfaction Index

The LSI investigates broader existential themes, such as the achievement of life goals (153). This questionnaire is administered as a series of twenty statements typed individually onto cards which the subject sorts into three piles, signifying agreement, disagreement or uncertainty. The responses are scored as 0 for a negative response, 2 for a positive response and 1 for an uncertain response. Thus, a range of scores from 0 to 40 is possible, a higher score reflecting a subject's more positive attitude to life.

Quality of Life Thermometer

The Quality of Life Thermometer (QoLTH), a visual analogue scale adapted from Torrance, is a summary measure of perceived quality of life (154). The scale was presented to the patient depicted as a standard thermometer. The thermometer was graded from 0 representing "death" to 100 representing "good health". Patients were asked to rate their present quality of life between the two anchor points. The thermometer also gave subjects the option of rating their HR-QoL as sub-zero, worse than death.

Previous Australian Quality of Life Studies

Two Australian groups were available for comparison with the COPD patients at FMC. A random sample of the population, aged 65-74 years, residing in the Flinders Medical Centre catchment region of the southern Adelaide metropolitan area, was used as a comparison group to provide normal quality of life ratings for the NHP.(154) South Australian norms for the SF-36 for males and females aged 65-74 years were obtained for the first time by the Behavioural Epidemiology Unit of the South Australian Health Commission by including the questionnaire in their 1994 Spring Health Omnibus Survey. This survey involved a multistage, systematic, clustered area sample, with 75% of the sample being selected from the Adelaide metropolitan area and the remainder from country centres with a population of 1,000 or more (155). There have been no previous reports available for the CRQ for an Australian population.

The scores for all areas of the NHP except pain were considerably worse for the FMC COPD patients compared with the normal elderly population. A comparison between the NHP and the MOS SF-36 and South Australian normal values is reported in detail in Chapter 8.

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

CHAPTER 3

Oxygen concentrators--an economical new technology

A J Crockett

Respiratory Unit, Flinders Medical Centre, Bedford Park, SA 5042

Medical Journal of Australia 1985; 142(9): 512-3.

STATEMENT OF AUTHORSHIP

Title of Paper: Oxygen concentrators--an economical new technology

***Medical Journal of Australia*, 1985; 142(9): 512-3.**

Name of candidate: Alan J Crockett

Introduced oxygen concentrators into Australia, wrote manuscript and acted
as corresponding author.

Signed

Date.....*30/6/05*.....

The early experiences in setting up a home or long term oxygen program for patients with chronic lung disease at Flinders Medical Centre in South Australia identified numerous problems associated with the method of delivery of this intervention. At that time oxygen was contained in heavy steel cylinders ranging in capacity from 490 litres for the "C" cylinders weighing approximately 3.3 kilograms to 4,100 litres for the "E" cylinders that weighed 22 kilograms.

The larger "E" cylinder was the most common method of providing an oxygen source to the patient at home. These cylinders were bulky, the contents were under high pressure and almost impossible for the patient or their carer to move from one location to another within the home. There were problems associated with this method of oxygen delivery that are also discussed in Chapter 5.

In the mid 1970's a device known as an oxygen contractor was developed which 'sieved' oxygen from room air and provided a continuous supply of low flow oxygen. These devices contained a compressor powered by electricity and Molecular Sieve 5A material. I had the opportunity to study use and availability of oxygen concentrators in the United States and United Kingdom during visits to these countries in 1978 and 1980 respectively. Subsequently, the Flinders Medical Centre Respiratory Unit evaluated the effectiveness of oxygen concentrators under Australian conditions.

The paper presented in this chapter reports these initial results. This preliminary work prompted endeavours to introduce oxygen concentrators more widely throughout the country and to undertake a prospective study into the impact of home oxygen therapy in South Australia.

Crockett, A.J. (1985) Oxygen concentrators - an economical new technology.
Medical Journal Of Australia, v. 142 (9), pp. 512-513, 1985

NOTE: This publication is included in the print copy of the thesis
held in the University of Adelaide Library.

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

CHAPTER 4

Cost Centre Management: How it Helped Reduce Home Oxygen Costs

A J Crockett ¹, JH Alpers¹, JP Chalmers ²

¹ Respiratory Unit , Flinders Medical Centre, Bedford Park, SA 5042

² Department of Medicine, Flinders Medical Centre, SA 5042

Australian Health Review .1986; 9(1): 38-42.

STATEMENT OF AUTHORSHIP

Title of Paper Cost Centre Management: How it Helped Reduce Home Oxygen Costs

Australian Health Review, .1986, 9 (1): 38-42.

name of candidate. Alan J Crockett

Collected the data, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

Date

30/6/08

co-author name. JH Alpers

Provided data interpretation and manuscript evaluation.

Signed

.....

Date

5/11/04

co-author name JP Chalmers

Provided data interpretation and manuscript evaluation.

Signed

.....

Date

15.12.04

Crockett, A.J., Alpers, J.H. and Chalmers, J.P. (1986) Cost centre management: how it helped reduce home oxygen costs.

Australian Health Review, v. 9 (1), pp. 38-42, 1986

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

The continuing impact of home oxygen therapy for respiratory patients on a hospital budget.

A J Crockett ¹, JR Moss ², JH Alpers¹

¹ Respiratory Unit , Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Australian Health Review 1992; 15(3): 259-68.

STATEMENT OF AUTHORSHIP

Title of Paper The continuing impact of home oxygen therapy for respiratory patients on a hospital budget.

Australian Health Review, .1992, 15 (3): 259-68.

name of candidate. Alan J Crockett

Collected the data, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

Date

30/6/05

co-author name. JR Moss

Provided data interpretation and manuscript evaluation.

Signed

.....

Date

30-6-05

co-author name JH Alpers

Provided data interpretation and manuscript evaluation.

Signed

.....

Date

5/11/07

The results of this study gave rise to the evaluation of the impact of the total intervention, oxygen concentrators and portable that is reported in subsequent chapters of this thesis. The initial paper also highlighted the problem of funding home care therapy from teaching hospital budgets.

In the 1970's and up until the 1982/1983 financial year little was know about the costs of the developing home oxygen program since Flinders Medical Centre operated under a traditional hospital organizational model. There was central control of costs with little input or feedback to the departments or units that generated the costs. In 1982/1983 Flinders Medical Centre Administration took, what was then bold step of limited decentralization of the control of finances by Cost Centre Management. This involved Departmental Heads and staff in the decision making process..

The papers presented in this chapter reports on the impact of Cost Centre Management and how it helped identify to the physicians and other respiratory staff the cost implications of the home oxygen program. At this time there were no other Australian reports of how this form of management impacted on a clinical service. The information gained in this study also re-inforced the need for an ongoing evaluation of not only the costs but also the impact of this intervention on the survival and quality of life of patients with chronic lung disease. The second paper focused on the ongoing economic impact of the provision of long term oxygen therapy. It confirms the previous initial observations, that Cost-Centre Management is a useful method of identifying and controlling the cost

This paper documents the financial impact of switching from the traditional cylinders only method of supplying oxygen to patients to the use of oxygen concentrators. It also highlights the increase in the number of patients prescribed long-term oxygen therapy.

One strategy described to enhance patients' quality of life was the introduction of portable "C" size cylinders to allow mobility. The alternative, to supply a concentrator only, could lead to the patients being 'tied' to the machine or become a form of home detention. It was argued that not supplying portable cylinders was likely to have profound implications for the patients' mobility.

Crockett, A., Moss, J. and Alpers, J. (1992) The continuing impact of home oxygen therapy for respiratory patients on a hospital budget.
Australian Health Review, v. 15 (3), pp. 259-68, 1992

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

CHAPTER 5

Home oxygen therapy: an audit of survival

A J Crockett ¹, JH Alpers ¹, JR Moss²

¹ Respiratory Unit, Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Australian & New Zealand Journal of Medicine 1991; 21(2): 217-21.

STATEMENT OF AUTHORSHIP

Title of Paper: Home oxygen therapy: an audit of survival

Australian & New Zealand Journal of Medicine, 1991;21(2):217-21..

name of candidate. Alan J Crockett

Collected the data, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

.....Date *30/6/05*

co-author name. JH Alpers

Provided access to patients, data interpretation and manuscript evaluation.

Signed

.....

.....Date *5/11/04*

co-author name JR Moss

Helped in data interpretation and manuscript evaluation.

Signed

.....

.....Date *30-6-05*

The two randomised control trials for oxygen therapy (1, 2) suggested that chronic lung disease patients receiving long-term oxygen therapy had a survival advantage. Many physicians believed that this could be as much as 5 years of added life. In 1987 McKeon et al (9) briefly reported survival data for their patients. However, the main focus of their paper was an economic evaluation similar to that reported in Chapter 4.

The paper presented in this chapter reports the first detailed Australian survival data for patients receiving long-term oxygen therapy. It reports the retrospective audit of data for 186 patients who entered the FMC home oxygen program over an initial period of 9 years. Our results demonstrated that in spite of physiological similarities between our patients and the patients recruited into the NOTT and MRC studies, our patients' mortality rate was twice that of these landmark studies. We were able to confirm clinical impressions that survival of patients' with interstitial lung disease was significantly less than those with COPD. We also noted that females appeared to have a significantly longer survival than males in our COPD cohort.

We postulated at that time that the relatively poor survival might be due to the high level of co-morbidities in our patients. This observation is further explored in Chapter 16 of this thesis. These results also prompted the design of a prospective study that further investigated the impact of home oxygen on both survival and to further explore other important health outcomes such as quality of life of our patients.

This paper has been cited on at least 4 occasions in the peer-reviewed literature.

Crockett, A.J., Alpers, J.H. and Moss, J.R. (1991) Home oxygen therapy: an audit of survival.

Australian and New Zealand Journal of Medicine, v. 21 (2), pp. 217–221, April 1991

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.1111/j.1445-5994.1991.tb00445.x>

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

CHAPTER 6

Trends in chronic obstructive pulmonary disease mortality in Australia.

A J Crockett ¹, JM Cranston ¹, JR Moss ², JH Alpers¹

¹ Respiratory Unit , Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Medical Journal of Australia 1994; 161(10): 600-603.

STATEMENT OF AUTHORSHIP

Title of Paper: Trends in chronic obstructive pulmonary disease mortality in Australia.

Medical Journal of Australia 1994; 161(10): 600-603..

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

.....Date *30/6/05*

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript

Signed

.....

.....Date *24.2.05*

co-author name. JR Moss

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date *30-6-05*

co-author name JH Alpers

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date *5/11/06*

The results of the studies reported in previous chapters highlighted the need to attempt to identify the prevalence of chronic lung disease in Australia. At that time only one paper had been published in medical literature that related to mortality of chronic obstructive pulmonary disease. However, there had been several publications reporting on Australian asthma mortality data.

Christie's 1971 paper reported on the increases in chronic bronchitis mortality between 1940 and 1964(156). This Chapter reported on mortality rates from 1964 to 1990 taking into consideration changes in International Classification of Diseases (ICD) codes and the fact that chronic bronchitis had been included in the then current definitions of chronic obstructive pulmonary disease. At that time we hypothesised that female COPD mortality would equal male mortality by the year 2005.

At the time of writing the Australian Bureau of Statistics respiratory mortality data is available only up to 1994 that prevents testing of the hypothesis.

This paper has been cited 5 times in the peer-reviewed literature.

Crockett, A.J., Cranston, J.M., Moss, J.R. and Alpers, J.H. (1994) Trends in hospitalization with chronic obstructive pulmonary disease mortality in Australia *Medical Journal of Australia*, v. 161 (10), pp. 600-603, 1994

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

CHAPTER 7

The effects of home oxygen therapy on hospital admission rates in chronic obstructive airways disease.

A J Crockett ¹, JR Moss ², JM Cranston ¹, JH Alpers¹

¹ Respiratory Unit, Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Monaldi Archives of Chest Disease 1993;48(5): 445-446

STATEMENT OF AUTHORSHIP

Title of Paper Effects of long-term oxygen therapy on quality of life and survival in chronic airflow limitation

Monaldi Archives of Chest Disease 1993 48(5):445-4466

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....Date..... 30/6/05

co-author name. JR Moss

Provided data interpretation and manuscript evaluation

Signed

.....Date..... 30-6-05

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript.

Signed

.....Date..... 24.2.05

co-author name JH Alpers

Provided data interpretation and manuscript evaluation.

Signed

.....Date..... 5/4/04

The collection of papers presented in this chapter describes the initial evaluation of data from the longitudinal study of the impact of long-term oxygen therapy. The results were reported in full as invited oral presentations at the 2nd International Conference on Advances in Pulmonary Rehabilitation and Management of Chronic Respiratory Failure. Venice, Italy, November 4 - 7, 1992, and further conferences under the same banner held in Freiberg, Germany in 1994 and Florence, Italy in 1996.

In 1968 Professor Tom Petty reported that it was "...apparent that oxygen drastically reduced the number of necessary hospital days..." (93) when he reported a case series of twenty patients with COPD. He later presented a photograph of the size of medical records before and after the commencement of long-term oxygen therapy in his chapter on the Historical Perspective on Long-term Oxygen therapy in Volume 81 of the Lung Biology in Health and Disease (157).

The data presented in this paper demonstrated a reduction in hospital admissions after 26 patients entered the long-term oxygen therapy program compared to the 12-month period prior to entering the program. Extensive searches of the literature suggest that this is the first published paper that has reported quantitatively the reduction in the number of admissions and bed days in a twelve month period pre and post commencement of therapy.

Crockett, A.J., Moss, J.R., Cranston, J.M. and Alpers, J.H. (1993) The effects of home oxygen therapy on hospital admission rates in chronic obstructive airways disease. *Monaldi archives for chest disease*, v. 48 (5), pp. 445-6, Oct 1993

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

Initial trends in quality of life and survival in CAL patients on domiciliary oxygen therapy

A J Crockett¹, JM Cranston¹, JR Moss², JH Alpers¹

¹ Respiratory Unit, Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Monaldi Archives of Chest Disease 1996; 51(1): 64-71.

STATEMENT OF AUTHORSHIP

Title of Paper Initial trends in quality of life and survival in CAL patients on domiciliary oxygen therapy

Monaldi Archives of Chest Disease 1996;51(1):64-71.

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

.....Date *20/6/05*

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript

Signed

.....

.....Date *24.2.05*

co-author name. JR Moss

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date *30-6-05*

co-author name JH Alpers

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date *5/11/04*

This chapter presents the paper documenting the initial results from the longitudinal study into the impact of long-term oxygen therapy on the survival and quality of life of patients with chronic obstructive pulmonary disease.

This paper was unique in that it was the first publication to report quality of life data for 45 Australian COPD patients using the generic Nottingham Health Profile, the disease-specific Chronic Respiratory Disease Questionnaire and the Life Satisfaction Index. It also describes changes in the various domains of quality of life at 3 and 6 months after the commencement of long-term oxygen therapy.

Earlier reports of the impact of long term oxygen therapy on quality of life had used the Sickness Impact Profile from the NOTT study which suggested that there could be several different interpretations (158). Firstly, there may not be any significant health related quality of life benefits from long-term oxygen therapy. Secondly, survival and quality of life were not related in these patients. Thirdly, the methods used to measure quality of life were not sensitive to change. The relatively small number of patients and length of follow-up questioned the validity of the results relating to the quality of life instruments used, and their ability to detect change.

This paper has been cited 5 times in peer-reviewed literature.

Crockett, A.J., Cranston, J.M., Moss, J.R. and Alpers, J.H. (1996) Initial trends in quality of life and survival in CAL patients on domiciliary oxygen therapy. *Monaldi archives for chest disease*, v. 51 (1), pp. 64-71, Feb 1996

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease
Alan J Crockett

**Effects of long-term oxygen therapy on quality of life and survival in
chronic airflow limitation.**

A J Crockett ¹, JM Cranston ¹, JR Moss ², JH Alpers¹

¹ Respiratory Unit , Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Monaldi Archives of Chest Disease 1999; 54(2): 193-196.

STATEMENT OF AUTHORSHIP

Title of Paper The effects of home oxygen therapy on hospital admission rates
in chronic obstructive airways disease.

Monaldi Archives of Chest Disease 1993 48(5):445-446..

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

.....Date 2/6/05.....

co-author name. JR Moss

Provided data interpretation and manuscript evaluation

Signed

.....

.....Date 30-6-05.....

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript.

Signed

.....

.....Date 24.2.05.....

The paper presented in this chapter reports on the initial 12 month prospective evaluation of the impact of long-term oxygen therapy of the health related quality of life and survival of COPD patients. At the time of writing 114 COPD patients had been recruited into the study. There were almost equal numbers of males (N=59) and females (n=55). This was unique at the time as most studies reported had included a larger number of male patients.

We reported that the overall survival of our patients was less than in the original randomized controlled trials. However, it was noted that the survival data was similar to that found in large national registers of long-term oxygen therapy (107).

There was a female survival advantage that supported results from France and Japan (159, 160). We hypothesised that females were better at adapting to the disease and to the intervention. A second possible hypothesis was that the natural history of COPD may be different in females than males. The most significant HR-QOL was that fatigue was significantly improved in both males and females after the introduction of the intervention.

This paper has been cited 12 times in the peer-reviewed literature.

Crockett, A.J., Cranston, J.M., Moss, J.R. and Alpers, J.H. (1999) Effects of long-term oxygen therapy on quality of life and survival in chronic airflow limitation. *Monaldi archives for chest disease*, v. 54 (2), pp. 193-6, April 1999

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

Non-conventional indications of long-term oxygen therapy: oxygen therapy during exercise.

A J Crockett ¹, JM Cranston ¹

¹ Respiratory Unit, Flinders Medical Centre, Bedford Park, SA 5042

Monaldi Archives of Chest Disease 1999; 54(1): 72-74.

STATEMENT OF AUTHORSHIP

Title of Paper The effects of home oxygen therapy on hospital admission rates
in chronic obstructive airways disease.

Monaldi Archives of Chest Disease 1993 48(5):445-446..

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

.....Date 2/6/05

co-author name. JR Moss

Provided data interpretation and manuscript evaluation

Signed

.....

.....Date 30-6-05

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript.

Signed

.....

.....Date 24.2.05

Crockett, A.J. and Cranston, J.M. (1999) Nonconventional indications of long-term oxygen therapy: oxygen therapy during exercise.
Monaldi archives for chest disease, v. 54 (1), pp. 72-4, February 1999

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

CHAPTER 8

The MOS SF-36 health survey questionnaire in severe chronic airflow limitation: a comparison with the Nottingham Health Profile

A J Crockett ¹, JM Cranston ¹ , JR Moss ² , JH Alpers¹

¹ Respiratory Unit , Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Quality of Life Research 1996; 5(3): 330-338.

STATEMENT OF AUTHORSHIP

Title of Paper The MOS SF-36 health survey questionnaire in severe chronic airflow limitation: a comparison with the Nottingham Health Profile .

Quality of Life Research 1996; 5(3):330-338.

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

.....Date *30/6/05*

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript

Signed

.....

.....Date *24.2.05*

co-author name. JR Moss

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date *30-6-05*

co-author name JH Alpers

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date *5/11/04*

In 1992 Alonso et al (161) first reported the quality of life of non-oxygen dependent COPD using the Spanish version of the Nottingham Health Profile (NHP). He reported that COPD had worse energy, physical mobility and sleep NHP scores than the general Spanish population. Three years after Ware and Sherbourne (142) described the conceptual framework and item selection for the SF-36, Mahler and MacKowiak reported his evaluation of the Short Form 36 –Item (SF-36) questionnaire in COPD patients (166).

The paper presented in this chapter is the first description of quality of life of COPD patients in Australia using generic quality of life questionnaires. It is also the first in the international literature to compare the results of quality of life measures on oxygen dependent COPD patients using both the NHP and SF-36 generic questionnaires. The results sharply contrasted with the relatively mild impairment shown in other studies (116). We also described discrepant observations in several domains between the two questionnaires, in particular, the measures of subjective mental health and emotion. We hypothesised that the SF-36 and NHP should be used conjointly in order to capture all aspects of the impact of COPD on health related quality of life.

This paper has been cited 12 times in the peer-reviewed literature.

Crockett, A.J., Cranston, J.M., Moss, J.R. and Alpers, J.H. (1996) The MOS SF-36 health survey questionnaire in severe chronic airflow limitation: comparison with the Nottingham health profile.
Quality of Life Research, v. 5 (3), pp. 330-338, June 1996

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.1007/BF00433917>

CHAPTER 9

Program budgeting and marginal analysis: a case study in chronic airflow limitation

A J Crockett ¹, JM Cranston ¹, JR Moss ², P Scown³, G Mooney⁴, JH Alpers¹

¹ Respiratory Unit, Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

³. Corporate and Clinical Support Services, Flinders Medical Centre, Bedford Park, SA5042.

⁴. Department of Public Health and Community Medicine, University of Sydney

Australian Health Review 1999; 22(3): 65-77.

STATEMENT OF AUTHORSHIP

Title of Paper Program budgeting and marginal analysis: a case study in chronic airflow limitation

Australian Health Review 1999; 22(3):65-77.

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

.....Date *30/6/05*

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript.

Signed

.....

.....Date *24.2.05*

co-author name. JR Moss

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date *30-6-05*

co-author name P Scown

Acted as guarantor for the study and manuscript evaluation

Signed

.....

.....Date *7/10/04*

Dr Paul Scown
Chief Executive
Melbourne Health

co-author name G Mooney

Signed

.....

.....Date 18/10/14

Provide expert advise on PBMA methodology and manuscript evaluation

co-author name JH Alpers

Provided manuscript evaluation.

Signed

.....

.....Date 5/14/14

The Respiratory Unit at Flinders Medical Centre had a long-term commitment to enhancing the effectiveness and efficiency of its services to all patients with respiratory disease. It was due to this commitment that the Operations Committee of Flinders Medical Centre was chosen as one of three areas suitable to undertake the economic analysis titled Program Budgeting and Marginal Analysis.

This project was structured on the disease group chronic obstructive pulmonary disease COPD as this represented the major proportion of the workload of the Respiratory Unit. It also represented at the time approximately 4% of all admissions to FMC. The project was based in a clinical service and clinical decision makers including patients had a key role. This project was one of the first to be undertaken in South Australia using the PBMA methodology. It is of note that the other areas identified by the Operations Committee opted not to complete the study.

The paper presented in this chapter represents a summary of a much larger report submitted to the then South Australian Health Commission. This larger report was deposited in the National Library of Australia (LD01/10140) at the request of the government authorities.

Crockett A., Cranston J. and Moss J., Scown, P., Mooney, G. and Alpers, J.H. (1999)
Program budgeting and marginal analysis: a case study in chronic airflow limitation.
Australian Health Review, v. 22 (3) ,pp. 65–77, 1999

NOTE: This publication is included in the print copy of the thesis
held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.1071/AH990065>

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

CHAPTER 10

Domiciliary oxygen for chronic obstructive pulmonary disease

A J Crockett ¹, JM Cranston ¹ JR Moss ² JH Alpers¹

¹ Respiratory Unit, Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Cochrane Database of Systematic Reviews 2000(4): CD001744

The Cochrane Database of Systematic Reviews

The Cochrane Library. Copyright 2003, The Cochrane Collaboration

Volume (1) 2003 [no page #]

Domiciliary oxygen for chronic obstructive pulmonary disease [Review]

Crockett, AJ; Cranston, JM; Moss, JR; Alpers, JH

Date of Most Recent Update: 23-January-2003

Date of Most Recent Substantive Update: 8-June-2000

[†]Cochrane Airways Group.

Assoc Prof. Alan Crockett, Associate Professor and Reader in Respiratory Medicine, Respiratory Unit, Flinders Medical Centre, Bedford Park, Adelaide, South Australia 5042, AUSTRALIA. Phone: + 61 8 8204-4622. Fax: + 61 8 8204-5632, E-mail: alan.crockett@flinders.edu.au

Outline

- [Abstract](#)
- [Internal sources of support to the review](#)
- [External sources of support to the review](#)
- [Most recent changes](#)
- [Date of last minor update](#)
- [Date new studies sought but none found](#)
- [Date new studies found and included or excluded](#)
- [Issue next stage](#)
- [Background](#)
- [Objectives](#)
- [Criteria for considering studies for this review](#)
 - [Types of participants](#)
 - [Types of intervention](#)
 - [Types of outcome measures](#)
 - [Types of studies](#)
- [Search strategy for identification of studies](#)
- [Methods of the review](#)
- [Description of the studies](#)
- [Methodological qualities of included studies](#)
- [Results](#)
- [Discussion](#)
- [Conclusions](#)
 - [Implications for practice](#)
 - [Implications for research](#)
- [Potential conflict of interest](#)
- [Acknowledgements](#)
- [Contribution of Reviewer\(s\)](#)
- [Synopsis](#)
- [Table of comparisons](#)
- [Table of comparisons](#)
- [Table of comparisons](#)
- [Table of comparisons](#)
- [Characteristics of included studies](#)
- [Characteristics of excluded studies](#)
- [References to studies included in this review](#)
- [References to studies excluded in this review](#)

Graphics

- 01.01.00 Mortality...
- 02.01.00 Mortality a...
- 03.27.00 Mortality a...
- 04.01.00 Mortality (...)
- 04.02.00 Mortality b...

Abstract

Background: Domiciliary oxygen therapy has become one of the major forms of treatment for hypoxaemic chronic obstructive pulmonary disease (COPD) patients.

Objectives: To determine the effect of domiciliary oxygen therapy on survival and quality of life in patients with COPD.

Search strategy: Randomised controlled trials (RCTs) were identified using the Cochrane Airways Group COPD register using the search terms: home OR domiciliary AND oxygen.

Selection criteria: Any RCT in patients with hypoxaemia and COPD that compared long term domiciliary or home oxygen therapy with a control treatment.

Data collection and analysis: Data extraction was performed independently by two reviewers.

Main results: Five randomised controlled trials were identified. Data was aggregated from two trials of the treatment of nocturnal oxygen therapy in patients with mild to moderate COPD and arterial desaturation at night. Data could not be aggregated for the other three trials because of differences in trial design and patient selection. Natt 1980: continuous oxygen therapy versus nocturnal oxygen therapy: there was a significant improvement in mortality after 24 months (Peto odds ratio 0.45, 95% confidence interval 0.25 to 0.81). MRC 1981: domiciliary oxygen therapy versus no oxygen therapy: there was a significant improvement over five years in mortality in the group receiving oxygen therapy (Peto odds ratio 0.42, 95% confidence interval 0.18 to 0.98). In two studies of nocturnal oxygen versus no oxygen in patients with COPD and arterial desaturation at night: there was no difference in mortality between treated and non treated groups for either trial or when the trials were aggregated. In one study of long term oxygen versus no oxygen in moderate hypoxaemia: there was no effect on survival for up to three years of follow up. An update search conducted in January 2003 did not identify any further studies for inclusion in the review.

Conclusions: Long term oxygen therapy improved survival in a selected group of COPD patients with severe hypoxaemia (arterial PO₂ less than 8.0 kPa). Long term oxygen did not appear to improve survival in patients with moderate hypoxaemia or in those with only arterial desaturation at night.

Internal sources of support to the review

* Australasian Cochrane Centre AUSTRALIA

* NHS Research and Development UK

External sources of support to the review

*

Most recent changes

Inclusion of an additional RCT by Chaouat 1999 (titled "A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients.")

Date of last minor update

23 January, 2003

Date new studies sought but none found

1 January, 2003

Date new studies found and included or excluded

2000, 5, 24

Issue next stage

Issue 4, 2003

Background

Patients with chronic lung disease develop chronic hypoxaemia which is related to the progression of their underlying condition. Over the last 20 years domiciliary oxygen therapy has become one of the major forms of treatment for hypoxaemic chronic obstructive pulmonary disease (COPD) patients.

Objectives

To determine the effect of domiciliary oxygen therapy on survival and quality of life in patients with COPD and hypoxaemia.

Criteria for considering studies for this review

Types of participants

Adults with COPD, also known as Chronic Airflow Limitation (CAL), Chronic Obstructive Airways Disease (COAD) or Chronic Airflow Obstruction (CAO), who received home oxygen therapy in the community. The majority of the patients had chronic hypoxaemia, arterial oxygen tension (PaO₂) < 7.3 kPa (55 mm Hg), but some of the patients had a PaO₂ > 7.3 kPa at rest with evidence of nocturnal hypoxaemia or desaturation with exercise.

Types of intervention

The intervention in the active treatment group covered all forms of long term domiciliary oxygen therapy including provision of oxygen using cylinders, concentrators or liquid oxygen therapy. In the control group, the intervention was either placebo air by the same method of delivery or no specific intervention.

Types of outcome measures

1. Survival
2. Health related quality of life as measured by a validated instrument.
3. Improvement in physiological parameters.

Types of studies

Any randomised controlled trial (RCT) in patients with hypoxaemia and COPD that compared long term domiciliary or home oxygen therapy with a control group.

Search strategy for identification of studies

RCTs were identified using the Cochrane Airways Group COPD register using the search terms: (home OR domiciliary AND oxygen).

Following this, the bibliographies of each RCT were searched for additional papers that may have contained RCTs. Authors of identified RCTs were contacted but additional data was not available. In addition, companies who supply the oxygen delivery devices and members of the International Respiratory Care Club were contacted for unpublished studies.

Methods of the review α

All RCTs that appeared potentially relevant were assessed by three individuals, who then independently selected the trials for inclusion in this review. Disagreement was resolved by consensus.

All trials were entered and scored as double blind, single blind or not blinded/not known.

Data for the trials were extracted by two reviewers (AB and JC). Authors were contacted in an attempt to obtain raw data from the trials.

STATISTICAL CONSIDERATIONS

Subgroup analysis included where possible

1. A comparison of male with female patients.
2. Continuous oxygen therapy versus nocturnal oxygen therapy
3. Oxygen therapy versus no oxygen therapy.
4. Nocturnal oxygen therapy versus room air for arterial oxygen desaturation during sleep.
5. Long term oxygen therapy versus no oxygen therapy for moderate hypoxaemia.

Description of the studies α

See table of included studies for a description of the studies.

1. Continuous oxygen therapy or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease (NOIT 1980).
2. Long term oxygen therapy versus no oxygen therapy (MRC 1981) in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema.
3. Nocturnal oxygen therapy 3 l/minute versus room air 3 l/minute (Eiseler 1992) for patients with COPD and nocturnal sleep desaturation but resting daytime PaO₂ greater than 60 mm Hg (8 kPa).
4. Long term oxygen therapy plus conventional treatment in patients with COPD and moderate hypoxaemia versus conventional treatment alone (Crockett 1997).
5. Nocturnal oxygen therapy in COPD patients with mild to moderate daytime hypoxaemia and nocturnal sleep desaturation (Cluett 1999).

Methodological qualities of included studies α

DATA ANALYSIS

The data from the two studies of nocturnal oxygen in mild to moderate hypoxaemia was aggregated. None of the data from the other studies could be aggregated into a meta-analysis because of variation in treatment and types of patients recruited.

The data for the Cluett 1999 study was analysed on an intention to treat basis due to some patients in both the intervention and control groups deteriorating to the extent that they required long term oxygen therapy during the follow-up period.

Results α

Seven abstracts were identified from the comprehensive searches of the data bases and five

were selected for possible inclusion in the review. The full text was obtained for all of the abstracts.

Three papers were found to be reports on various aspects of one RCT (NOTT 1980). One of these was excluded as it contained baseline data only. The physiological data from another of these papers was combined with data from the original NOTT 1980 study report.

Five RCTs (six papers) were identified as being suitable for inclusion in this review.

An update search conducted in January 2003 did not identify any new studies for inclusion in the review.

CONTINUOUS OXYGEN THERAPY VERSUS NOCTURNAL OXYGEN THERAPY (NOTT 1980)

A total of 1,043 patients from six centres were screened for inclusion in the study. Eight hundred and nine patients were excluded for a variety of reasons including other major concomitant disease, refusal to participate and patients who had previous oxygen therapy or PaO₂ greater than 59 mm Hg (7.9 kPa). The study was not blinded.

Two hundred and three patients with hypoxaemic chronic obstructive lung disease were randomly allocated to nocturnal oxygen therapy (n=102) or continuous oxygen therapy (n=101) at a flow-rate of 1 to 4 litres per minute. The oxygen source was an oxygen concentrator, liquid oxygen or compressed gas. The mean age was 65.7 years in the nocturnal oxygen therapy group and 65.2 years in the continuous oxygen therapy group. Most patients were male, 80.4% in the nocturnal oxygen therapy group and 77.2% in the continuous oxygen therapy group.

The survival at 12 months was not significant (Peto Odds Ratio 0.53; 95% CI: 0.25 to 1.11). At 24 months there was a significant improvement in mortality (Peto Odds Ratio 0.45; 95%CI: 0.25 to 0.81) for the continuous oxygen treatment group.

In this RCT, quality of life parameters and some physiological variables were studied, but the numbers of patients in each group were not defined and could not be assessed using this meta-analysis protocol. However, in the Timm's report of the NOTT 1980 study, no significant difference was found between the treated and nocturnal groups of patients for the physiological parameters; right atrial pressure, pulmonary capillary wedge pressure, cardiac index and right ventricular stroke work index. However, the continuous oxygen therapy group was reported to show improvement in stroke volume index, pulmonary vascular resistance and pulmonary artery pressure.

The study speculated that those patients most likely to benefit from continuous oxygen therapy would have relatively severely impaired quality of life and brain dysfunction but relatively mild disturbances of pulmonary haemodynamics and exercise capacity.

OXYGEN THERAPY VERSUS NO OXYGEN THERAPY (MRC 1981)

This controlled trial of long term domiciliary oxygen therapy took place in three centres in the United Kingdom. Eighty seven patients with a diagnosis of chronic bronchitis and emphysema, were randomized to receive oxygen therapy or no oxygen (controls). The study was not blinded. Patients were enrolled in the study if they had a PaO₂ of between 40 and 60 mm Hg (5.3 and 8 kPa) and one or more recorded episodes of heart failure with ankle oedema and so were highly selected. Thirty three men and 9 women received oxygen therapy for at least 15 hours a day at a flow-rate of a minimum of 2 litres/minute. Of the 43 patients who received oxygen 8 received liquid oxygen therapy and all but one of patients (total number not disclosed) in one centre received oxygen via a concentrator. The remaining subjects received oxygen from cylinders. A total of 33 men and 12 women formed the control group.

Mean (range) age was 58.2 (44-69) years for the male treated group, 56.2 (42-68) years for the male control group, 59.4 (55-67) years for the female treated group and 59.3 (50-69) years for the female controls.

Mean baseline FEV1 was 0.76 litres and 0.58 litres for the treated male and female groups and 0.65 litres and 0.63 litres for the control male and female groups. Mean baseline FVC was 1.92 litres and 1.31 litres for the treated male and female groups and 1.88 litres and 1.46 litres for the control male and female groups. Mean baseline PaO2 was 50.4 mm Hg (6.7 kPa) and 49.4 mm Hg (6.6 kPa) for the treated male and female groups and 51.5 mm Hg (6.9 kPa) and 51.8 mm Hg (6.9 kPa) for the control male and female groups.

There was an improvement over five years in mortality in the group receiving oxygen therapy (Peto Odds Ratio 0.42, 95%CI: 0.18 to 0.98). However, there was no difference in mortality for male patients in both treated and control groups up to 500 days from commencement of treatment. In female patients, mortality was improved for the oxygen-treated group from the commencement of treatment. However, the number of female patients in each of the treated and control groups was small (n=9 and 12).

Physiological variables could not be assessed.

The study found that the male subjects most likely to benefit from oxygen therapy had a sum of the red cell mass and PaCO2 less than 98.

NOCTURNAL OXYGEN 3 l/min VERSUS ROOM AIR 3 l/min (Fletcher 1992)

Thirty eight patients with COPD and nocturnal sleep desaturation agreed to participate in this double-blind RCT. A further 13 patients with similar baseline pulmonary function who did not desaturate were also followed up but not randomized. In the control group of 19 patients, 6 patients died and 4 were excluded (2 withdrew, 1 developed daytime hypoxaemia, 1 was noncompliant). Of the original 19 treated subjects, 6 developed significant daytime hypoxaemia, 1 developed worsening of sleep apnoea and there were 5 deaths. The remaining 16 subjects were randomized to receive nocturnal oxygen therapy (n=7) or sham treatment (n=9).

Oxygen was supplied in the active group by an oxygen concentrator. The control group received gas from an oxygen concentrator rendered ineffective. However, some control group patients received an oxygen concentration of 25% rather than the ambient concentration of 21%, equivalent to an inspired O2 tension of approximately 30 mm Hg (4 kPa) greater than if they had received room air. Mean age in the control group was 61.2 years and mean age in the oxygen treated group was 62.1 years. The gender of the subjects was not given.

Physiological parameters could not be assessed.

There was no difference in mortality after 36 months between the oxygen treated and sham treated groups. However, the possibility of a Type-2 error occurring could not be rejected due to the small study size although the point estimate of mortality was very close to the odds ratio of 1.0.

LONG TERM OXYGEN THERAPY VERSUS NO OXYGEN THERAPY IN MODERATE HYPOXAEMIA (Gorecki 1992)

One hundred and thirty five patients with COPD and moderate hypoxaemia referred to nine regional centres in Poland were included in this unblinded RCT. Patients with concomitant disease that might impact on survival were excluded from the study.

Sixty seven patients, 52 males 15 females, mean age 62.4 years formed the control group and 68 patients, 51 males 17 females, mean age 60.1 years, formed the treatment group. Both treated and control groups received "usual treatment" which consisted of bronchodilators, antibiotics, corticosteroids and diuretics as required. The oxygen group received oxygen from

an oxygen concentrator at a flow-rate that raised their resting PaO₂ greater than 8.7 kPa (65 mm Hg). The patients were followed for three years or until death.

No difference in mortality during the study period was found between COPD patients with moderate hypoxaemia with conventional treatment plus long term oxygen therapy versus conventional treatment only. In the intervention group, duration of oxygen therapy (over 15 hours per day) did not affect survival.

Physiological parameters could not be assessed because these were not reported by treatment group.

NOCTURNAL OXYGEN THERAPY IN PATIENTS WITH MILD TO MODERATE HYPOXAEMIA (Chaouat 1999)

Seventy six patients with COPD and mild to moderate daytime hypoxaemia exhibiting significant nocturnal desaturation were randomized into this unblinded study. The patients were recruited from six hospital outpatient clinics of four European countries.

Thirty five patients, mean age 64 +/- 6 years, gender not defined, formed the control group and 41 patients, mean age 63 +/- 8 years the treatment group. Patients were excluded if they had a variety of comorbidities including left heart or congenital heart disease, interstitial lung disease, bronchiectasis, lung carcinoma or other severe disease that could influence survival. Patients with obstructive sleep apnea were also excluded. Patients in the treatment group were given concentrator oxygen for eight to ten hours per night at a flow rate usually of 2 litres per minute. The control group received no oxygen therapy.

There was no difference in mortality between the treated and control groups on an intention to treat basis.

Twelve patients in the nocturnal oxygen group and 10 control group patients deteriorated and required treatment with conventional long-term oxygen therapy during the follow-up period of from 2.5-60 months. Five of these patients subsequently died, two in the treated group and three in the control group. Nocturnal oxygen did not allow delay in the prescription of long-term oxygen therapy.

Pulmonary haemodynamics parameters could not be assessed due to limitations in the software design. However, no significant difference between treated and control groups in the evolution of any of these parameters was reported over a two year period.

Aggregating the Chaouat 1999 and Fletcher 1992 studies, a weighting of 61.3% was applied to the Chaouat 1999 study and 38.7% to the Fletcher 1992 study. There was no difference in mortality between the treated and control groups. The pooled Peto odds ratio moved closer to unity, 0.97 (95% confidence interval 0.41 to 2.31) than the individual odds ratios.

Discussion

Both the MRC 1981 and the Gorecka 1997 study treated subjects with COPD with long term oxygen therapy versus no oxygen therapy. However these two studies were not combined as the MRC 1981 included subjects with severe hypoxaemia (PaO₂ 5.3-8.0 kPa, 40-60 mm Hg) while the Gorecka 1997 study included subjects with moderate hypoxaemia (PaO₂ 7.4-8.7 kPa, 56-65 mm Hg). Although both studies included a small number of female subjects, survival was stratified by sex for the MRC 1981 study but not stratified for the Gorecka 1997 study.

SURVIVAL

Two of the five RCTs included in this review demonstrated a significant survival advantage for the selected COPD subjects receiving long term oxygen therapy. In the NOTT 1980 study there was a significant improvement in mortality for hypoxaemic COPD patients

after 24 months of treatment with continuous long term oxygen therapy over the nocturnal oxygen therapy group. In the [MRC 1981](#) study long term oxygen therapy produced a small but significant overall improvement in survival in both male and female patients with severe hypoxic cor pulmonale complicating chronic bronchitis and emphysema. However the authors reported a different survival response between males and females. Survival for treated and control male patients was similar until 500 days from the commencement of treatment ("Survivor effect"). However, the mortality of the control female patients was reported to be significantly greater than that of the treated females from the commencement of home oxygen therapy.

A numbers needed to treat (NNT) estimate (1/absolute relative risk) of 4.5 can be calculated for the [MRC 1981](#) study where the risk of death in the control group is 0.67, the relative risk for the oxygen treated group is 0.45, and the absolute risk reduction is 0.22. Thus, for the [MRC 1981](#) study, treating five patients with severe hypoxaemic COPD with long term oxygen therapy saved one life over the five year study period.

We found no evidence to suggest that nocturnal supplemental oxygen for COPD patients with nocturnal sleep desaturation but mild to moderate daytime hypoxaemia improved mortality.

Supplemental oxygen therapy for COPD patients with moderate hypoxaemia ([Gorecka 1997](#)) did not prolong survival.

The relatively small numbers of patients, the young age of participants and the lack of comorbidities in most of the above studies raises concerns about the applicability of the survival outcomes to current clinical situations. Patients with COPD fulfilling prescription guidelines for domiciliary home oxygen therapy appear to be older than the subjects included in these studies. The majority of these COPD patients have multiple comorbidities. The assumption that home oxygen therapy has a beneficial effect in these patients has not been demonstrated.

QUALITY OF LIFE ISSUES

Quality of life and other health outcome variables e.g. physiological parameters could not be included in this review as the available software is unable, at this point in time, to analyse rates of change.

Physiological variables should be considered intermediate outcomes while survival and quality of life should be considered as the more definitive outcomes. It is possible that statistically significant improvement in some physiological variables have little measurable impact on the subjects' perceived quality of life or survival.

The [MRC 1981](#) study reported that indicators such as general improvement in the sense of well-being, improved appetite, and general alertness were frequently found in those patients treated with oxygen therapy. However, no data was given. The [NOTT 1980](#) study reported neuropsychological deficits in hypoxic COPD patients groups and observed small improvements in neuropsychologic function and quality of life when data from all patients was combined.

LIMITATIONS OF THE STUDIES

This systematic review has highlighted several problems with the patient selection and study design. Only one of the studies was double blinded due to the inability to blind liquid oxygen therapy. The treatment regime for the control groups of the studies varied from none for the [Gorecka 1997](#) study, nocturnal oxygen therapy for the [NOTT 1980](#) study to sham treatment through a disabled oxygen concentrator equivalent to 25% oxygen therapy in the [Fletcher 1992](#) study. In the [Fletcher 1992](#) study this level of oxygen therapy for the control subjects may have confounded the results as this higher O₂ tension may have been reflected in the PaO₂ in this group. The control group in the [MRC 1981](#) study did not receive a sham treatment regime.

During follow-up in the Chaouat study (Chaouat 1999), 22 patients, (12 nocturnal oxygen and 10 control group) deteriorated and required treatment with long-term oxygen therapy. This treatment may have influenced their survival.

In the NOTT 1980 study the numbers of patients receiving the different modes of oxygen treatment were not given. In the MRC 1981 study there were some differences between treated and control groups at baseline. Females in the treated group appeared to have more compromised lung function than those of the control group while the reverse appeared to be apparent for the male patient groups. The mean number of hospitalizations and hospitalized days in the Eitelber 1992 study could not be included in this review as standard deviations were not given. The Gorecki 1997 study reported differences in studied variables by survivors and non survivors.

No data was reported in the two major studies (NOTT 1980 and MRC 1981) about the effects of continued or cessation of smoking or indeed if smoking status affected the outcomes. The mean arterial CO2 tension at baseline was higher in the MRC 1981 study than in the NOTT 1980 study. This did not appear to influence the results. Other known prognostic indicators such as body mass index were not discussed in either of the studies. The lack of exacerbation data is also a further limiting factor in interpreting the results.

Additional data has been sought from the authors of the studies.

This information if obtained will be used to update this review.

Conclusions

Implications for practice

Long term oxygen therapy improved survival in a selected group of COPD patients with severe hypoxaemia. Long term oxygen therapy did not appear to improve survival in patients with COPD and moderate hypoxaemia nor in COPD patients with nocturnal desaturation but resting daytime oxygenation above that to qualify for oxygen therapy.

Implications for research

The role of long term oxygen therapy in COPD with moderate hypoxaemia and or nocturnal desaturation requires further investigation with larger numbers of participants included in the studies.

Ethical concerns have been raised about the randomisation of patients to placebo and this may be a bar to obtaining more appropriate health status data about the effects of oxygen in more severely hypoxaemic subjects.

Potential conflict of interest

Nil

Acknowledgements

We wish to acknowledge the assistance provided by the Cochrane Airways Review Group staff (Steve Milan, Anna Bara and Jane Dennis) in identifying the trials from the register and obtaining copies of the papers and the editorial support from Dr Peter Gibson, Australian Coordinator of the Cochrane Airways Group. Anna Bara provided extra support in teaching us the correct way to use RevMan and helping us with data extraction.

Contribution of Reviewer(s)

AC and JC initiated the study. JM, AC and JC reviewed the trials.

JC was responsible for data entry and analysis. All reviewers participated in the discussion and interpretation of the results. AJC and JC wrote the paper, AC is guarantor for the study.

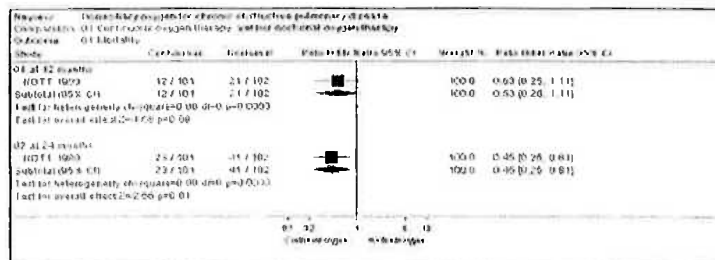
Synopsis

Long-term oxygen therapy at home through the night can increase survival in people with COPD who have low levels of oxygen in their arteries

Some people with chronic lung disease (COPD - chronic bronchitis or emphysema) have low levels of oxygen in their blood. Oxygen levels might be low all the time, or only at night when breathing slows during sleep. Some people use bottled oxygen through the night at home, to try and improve their breathing. The review of trials found that when people with COPD and low levels of blood oxygen did this for the long term, their survival rates improved. However, it did not lengthen survival of people whose oxygen levels were only moderately low, or only low at night.

Table of comparisons

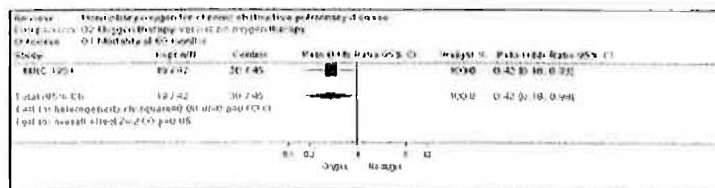
Fig 01 Continuous oxygen therapy versus nocturnal oxygen therapy



01.01.00 Mortality

Table of comparisons

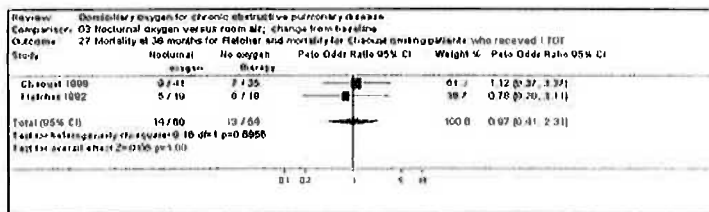
Fig 02 Oxygen therapy versus no oxygen therapy



02.01.00 Mortality at 60 months

Table of comparisons

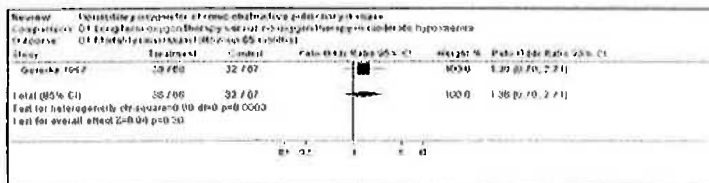
Fig 03 Nocturnal oxygen versus room air; change from baseline



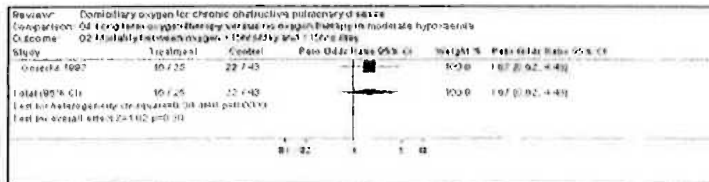
03.27.00 Mortality at 36 months for Fletcher and mortality for Chaouat among patients who received LTOT

Table of comparisons

Fig 04 Long term oxygen therapy versus no oxygen therapy in moderate hypoxaemia



04.01.00 Mortality (maximum follow-up 85 months)



04.02.00 Mortality between oxygen >15hrs/day and <15hrs/day

Characteristics of included studies

Study: Chaouat 1999

Methods: Randomized, unblinded, controlled study. Randomization by random sampling numbers, oxygen therapy to even numbers and no oxygen to odd numbers prospectively.

Participants: 76 COPD patients were randomized, 41 in the nocturnal oxygen group and 35 to the control group. 46 patients (24 treated and 22 control patients) were available for haemodynamic monitoring at 2 years.

Interventions: Nocturnal oxygen therapy, for 8-10 hours a night, at a flow to allow the nocturnal SaO2 to be constantly >90%.

Outcomes: Physiological parameters, Pulmonary haemodynamic parameters, survival

Notes:

Allocation concealment: A

Study: Fletcher 1992

Methods: Randomized, double blind, controlled trial. Randomization technique not described

Participants: 38 COPD patients with nocturnal desaturation, 9 patients were sham treated and 7 patients oxygen treated. Daytime PaO₂ greater than or equal to 60 mm Hg. Mean age 61.2 years in the sham treated group and 62.1 years in the oxygen treated group.

Interventions: Nocturnal oxygen or room air 3l/min supplied by home concentrators

Outcomes: Mortality, Physiological parameters, FEV₁, FVC, PAP

Notes:

Allocation concealment: B

Study: Gorecka 1997

Methods: Randomized, controlled study. Randomization schedules by computer generated random numbers

Participants: 135 patients with COPD and moderate hypoxaemia (PaO₂ 56-65 mmHg) referred to nine regional centres in Poland. Age between 40 and 80 years.

Interventions: Conventional treatment consisted of bronchodilators, (theophylline, B₂ agonists, and anticholinergic drugs). Antibiotics, diuretics and corticosteroids were prescribed at the discretion of the physician.

Long term oxygen therapy was given at a flow rate adjusted to raise PaO₂ above 65 mmHg.

Outcomes: Mortality

Notes:

Allocation concealment: A

Study: MRC 1981

Methods: Randomized controlled trial, (randomization method: random numbers), parallel study

Participants: 87 patients (66 males: 21 females), age < 70 years (range 42-69 years), FEV₁ <1.2l, PaO₂ between 40 and 60 mm Hg breathing air at rest, (two repeat measures 3 weeks apart).

Interventions: Long term domiciliary oxygen therapy versus no oxygen therapy.

Outcomes: Mortality, Physiological parameters of FEV₁, FVC, PaO₂ and PaCO₂

Notes:

Allocation concealment: A

Study: NOTT 1980

Methods: Randomized controlled trial. Randomization - computer generated

Participants: 203 patients, 101 received continuous oxygen therapy, (77.2% males) and 102 received nocturnal oxygen therapy, (80.4% males).

Entry criteria:

Clinical diagnosis of chronic obstructive lung disease, age > 35 years.

Hypoxemia PaO₂ < or = 55 mm Hg, PaO₂ < or = 59 plus one of the following;

Oedema, Hematocrit > or = 55%, Cor pulmonale on ECG: 3mm in leads II, III, aVF

Lung function: FEV₁/FVC < 70% after inhaled bronchodilator

TLC > or = 80% predicted

Age > 35 years

Interventions: Continuous oxygen therapy versus 12 hour nocturnal oxygen therapy 1-4l/min by oxygen concentrators or liquid oxygen systems or compressed gas.

Outcomes: Mortality

Physiological parameters; unable to be used as n is not defined.

Quality of life; unable to be used as n is not defined.

Cardiovascular parameters:

Right atrial pressure

Pulmonary artery pressure

Pulmonary wedge pressure

Cardiac index

Stroke volume index

Pulmonary vascular resistance

Right ventricular stroke index

Notes:

Allocation concealment: A

Characteristics of excluded studies

Study: Grant 1982

Reason for exclusion: Baseline data only from NOTT study patients.

References to studies included in this review

Chnouat 1999

Chnouat A, Weitzenblum E, Kessler R, Charpentier C, Ehrhart M, Schott R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients [see comments]. *European Respiratory Journal*

1999;14(5):1002-8. [[Medline Link](#)] [[Context Link](#)]

Fletcher 1992

Fletcher EC, Luckett RA, Goodnight-White SA, Miller CC, Qian W, Costarinos-Galarza C. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO₂ above 60 mm Hg. *American Review of Respiratory Disease* 1992;145(5):1070-6. [[Medline Link](#)] [[Context Link](#)]

Gorecka 1997

Gorecka D, Gorzelak K, Siwinski P, Tobiasz M, Zielinski J. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997;52(8):674-9. [[Medline Link](#)] [[Context Link](#)]

MRC 1981

Report of the Medical Research Council working party. Long-term domiciliary oxygen therapy in chronic hypoxic or pulmonary complicating chronic bronchitis and emphysema. *Lancet* 1981;1:681-5. [[Context Link](#)]

NOTT 1980

Nocturnal oxygen therapy trial group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. *Annals of Internal Medicine* 1980;93:391-8. [[Context Link](#)]

Timms RM, Khaja FU, Williams GW, and the Nocturnal Oxygen Therapy Trial Group. Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. *Annals of Internal Medicine* 1985;102:29-36. [[Medline Link](#)]

References to studies excluded in this review.:

Grant 1982

Grant I, Heaton RK, McSweeney AJ, Adams KM, Timms RM. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Archives of Internal Medicine* 1982;142(3):1470-6. [[Medline Link](#)]

Medical Subject Headings (MeSH): Human; Anoxemia/tp (therapy); *Home Care Services; Lung Diseases, Obstructive/tp (therapy); *Oxygen Inhalation Therapy; Randomized Controlled Trials; Self Care

Accession Number: 00075320-100000000-00883

Copyright (c) 2000-2003 Ovid Technologies, Inc.
Version: rel6.1.0, SourceID 1.7672.1.63

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

A review of long-term oxygen therapy for chronic obstructive pulmonary disease.

A J Crockett ¹, JM Cranston ¹ JR Moss ² JH Alpers¹

¹ Respiratory Unit, Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Respiratory Medicine 2001; 95(6): 437-443.

STATEMENT OF AUTHORSHIP

Title of Paper Domiciliary oxygen for chronic obstructive pulmonary disease

Cochrane Database of Systematic Reviews 2000(4):CD001744

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

.....Date.. 30/6/05

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript

Signed

.....

.....Date.. 25.2.05

co-author name. JR Moss

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date.. 30-6-05

co-author name JH Alpers

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date.. 5/11/04

The development of the Australian Centre for the Cochrane Collaboration by the late Professor Chris Silagy at Flinders Medical Centre in the late 1990's provided the opportunity to learn the various Cochrane Review techniques.

In 2000 we published the first version of the review of 'Domiciliary oxygen for chronic obstructive pulmonary disease'. The most frequently cited papers on long-term oxygen therapy are the two original randomised control trials(1, 2). Using the comprehensive Cochrane search techniques we were able to identify 6 papers reporting 5 randomized control trials on the subject. This chapter presents the most recent update our review that has been cited extensively.

For example the impact of the Cochrane Review to date has also been published Crockett AJ, Cranston JM, Moss JR, Alpers JH. A review of domiciliary oxygen therapy for Chronic Obstructive Pulmonary Disease. *Respiratory Medicine* 2001; 95 (6): 437-443 reported in this Chapter.

Crockett A., Cranston J., Moss J. and Alpers, J. (2001) A review of long-term oxygen therapy for chronic obstructive pulmonary disease.
Respiratory Medicine, v. 95 (6), pp. 437-443, June 2001

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.1053/rmed.2001.1064>

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

CHAPTER 11

An association between length of stay and co-morbidity in chronic airflow limitation

A J Crockett ¹, JM Cranston ¹ , JR Moss ² , JH Alpers¹

¹ Respiratory Unit , Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

International Journal of Quality Health Care 2000; 12(1): 41 – 46.

STATEMENT OF AUTHORSHIP

Title of Paper An association between length of stay and co-morbidity in chronic airflow limitation..

International Journal of Quality Health Care 2000;12(1):41 – 46.

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

.....Date.....

20/6/05

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript

Signed

.....

.....Date.....

24.2.05

co-author name. JK Moss

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date.....

30-6-05

co-author name JH Alpers

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date.....

5/11/07

The Respiratory Unit at FMC undertook a Program Budgeting and Marginal Analysis exercise in COPD that was reported in Chapter 9. The PBMA methodology includes identifying activities where changes in resource allocation may better meet social equity and economic efficiency. A major outcome of the PBMA was the identification of a relatively large number of elderly COPD patients with multiple co-morbidities that as a whole had a high rate of readmission to hospital in a 28-day period post-discharge for exacerbations of their disease.

The paper presented in this chapter reports on the factors that impacted on the length of in-patient stay for the index admission and the subsequent re-admission rates. In the period between December 1996 and March 1998 there were 2347 discharges where COPD was an active problem. There was substantial active co-morbid illness in these patients.

This paper has been cited 5 times in peer-reviewed literature.

Crockett A., Cranston J., Moss J. and Alpers, J. (2000) An association between length of stay and co-morbidity in chronic airflow limitation.
International Journal For Quality In Health Care, v. 12 (1), pp. 41-46, February 2000

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.1093/intqhc/12.1.41>

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

CHAPTER 12

Survival on long-term oxygen therapy in chronic airflow limitation: from evidence to outcomes in the routine clinical setting.

A J Crockett ¹, JM Cranston ¹ , JR Moss ² , JH Alpers¹

¹ Respiratory Unit, Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Internal Medical Journal 2002; 31(8): 448-454.

STATEMENT OF AUTHORSHIP

Title of Paper Survival on long-term oxygen therapy in chronic airflow limitation:
from evidence to outcomes in the routine clinical setting.

Internal Medical Journal 2002; 31(8): 448-454

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

.....Date *20/6/05*

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript

Signed

.....

.....Date *24.2.05*

co-author name. JR Moss

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date *30-6-05*

co-author name JH Alpers

Provided data interpretation and manuscript evaluation.

Signed

.....

.....Date *5/11/04*

The paper presented in this chapter confirmed the previous retrospective and interim prospective analyses of the data on COPD patients receiving long-term oxygen therapy at FMC (9, 11, 12, 14). This paper is a summary of a larger report of a study funded by the National Health and Medical Research Council Evidence-Based Clinical Practice Research Program Committee. This report has been deposited at the We were able National Library of Australia (LD01/10142).

This paper, using Kaplan-Meier product-limited estimators of survivorship function, reported on the survival of COPD patients prescribed LTOT at FMC compared to that of the original RCTs, and Swedish and Belgian COPD survival data obtained from the oxygen registers of those countries.

Survival for COPD patients prescribed LTOT at FMC was less than for the control arms of the previous RCTs except for the MRC female group, but comparable with recent overseas data from Belgium and Sweden. Crude survival of FMC COPD home oxygen patients was 75.1%, 51.3%, 18.9% and 1.1% at 1, 2, 5 and 10 years respectively. Females experienced longer survival than males(1, 2, 107, 108)..

Multivariate analysis using Cox's proportional hazards model indicated age, forced expiratory volume in 1 second (FEV₁), body mass index (BMI), and the number of co-morbidities were prognostic indicators for females, and BMI for males. A survival advantage existed for females using at least 19 hours of concentrator oxygen per day. The study concluded that, in routine clinical practice at FMC, survival of unselected COPD patients with multiple comorbidities was less than that reported in the original RCTs.

This paper has been cited 12 times in the peer-reviewed literature.

Crockett A., Cranston J., Moss J. and Alpers, J. (2001) Survival on long-term oxygen therapy in chronic airflow limitation: from evidence to outcomes in the routine clinical setting.
Internal Medicine Journal, v. 31 (8), pp. 448-454, November 2001

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.1046/j.1445-5994.2001.00103.x>

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

CHAPTER 13

The impact of anxiety, depression and living alone in chronic obstructive pulmonary disease.

A J Crockett ¹, JM Cranston ¹, JR Moss ², JH Alpers¹

¹ Respiratory Unit , Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Quality of Life Research 2002; 11(4): 309-316.

STATEMENT OF AUTHORSHIP

Title of Paper The impact of anxiety, depression and living alone in chronic obstructive pulmonary disease.

Quality of Life Research 2002; 11(4): 309-316.

name of candidate. Alan J Crockett

Conceived the research question, performed analysis, interpreted data, wrote manuscript and acted as corresponding author.

Signed

.....

Date.....

20/6/05

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and writing of the manuscript

Signed

.....

Date.....

24.2.05

co-author name. JR Moss

Provided data interpretation and manuscript evaluation.

Signed

.....

Date.....

30-6-05

co-author name JH Alpers

Provided data interpretation and manuscript evaluation.

Signed

.....

Date.....

5/11/04

In 1994 McCullum and colleagues reported an association between self-rated health and survival for older Australians (163). There had only been one previous report of a retrospective study showing an association between quality of life and survival in COPD(164).

The paper presented in this chapter reports of a study to determine whether aspects of health related quality of life as measured by the Guyatt Chronic Respiratory Disease questionnaire and living alone, were predictors of survival in patients receiving long-term oxygen therapy for COPD.

This was the first prospective study in the world literature to investigate the impact of psychosocial factors as independent predictors of mortality in COPD by gender.

Recently this paper has been cited in an American Thoracic Society review of home care for patients with COPD. McClure, J; Lewarski, J; Prentice, W; Selecky, PA; Turner, J; Weimer, M; Wijkstra, P. Statement on home care for patients with respiratory disorders. American Journal of Respiratory and Critical Care Medicine, 171 (12): 1443-1464 JUN 15 2005. The paper has been cited on 3 other occasions in the peer-reviewed literature.

Crockett, A.J., Cranston, J.M., Moss, J.R. and Alpers, J.H. (2002) The impact of anxiety, depression and living alone in chronic obstructive pulmonary disease. *Quality of Life Research*, v. 11 (4), pp. 309-316, June 2002

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.1023/A:1015517606893>

The Impact of Long Term Oxygen Therapy on South Australian with Chronic Lung Disease

Alan J Crockett

CHAPTER 14

The relative survival of COPD patients on long-term oxygen therapy in Australia

JM Cranston ¹, AM Nguyen ², A J Crockett ¹

¹ Respiratory Unit , Flinders Medical Centre, Bedford Park, SA 5042

² Department of Public Health, The University of Adelaide, SA 5005

Respirology 2004; 9(2): 237-242.

STATEMENT OF AUTHORSHIP

Title of Paper The relative survival of COPD patients on long-term oxygen therapy in Australia.

Respirology 2004;9(2):237-242.

name of candidate. Alan J Crockett

Conceived the research question, interpreted data, wrote manuscript.

Signed

.....

.....Date *20/6/04*

co-author name. JM Cranston

Collected the data, assisted with the data analysis, interpretation of the data and wrote the manuscript

Signed

.....

.....Date *24/3/05*

co-author name. AM Nguyen

Performed the relative survival analysis.

Signed

.....

.....Date *24/11/04*

The survival data for COPD patients reported in preceding chapters was extremely poor in spite of an intervention that is believed to increase survival. However, individual deaths in COPD patients may be associated with many other causes besides the disease in question. This can lead to bias in survival analysis.

The initial study of survival of COPD patients on home oxygen therapy was extended to a study of the relative survival of COPD patients on LTOT. Relative survival is defined as the ratio of the survival rate of the group under study compared to that of an age-matched normal population. Hakulinen's relative survival model takes into consideration the risk of death due to increasing age (165). There has been only one previous report of the relative survival of COPD patients on LTOT, a report from France (166).

Using this relative survival analysis, South Australian LTOT patients with COPD had worse outcomes than a group of French patients. The reason for this apparent difference in survival is unknown but may be due to differences in the genetic pool, the nature of the disease, treatment, or environmental or lifestyle factors. The difference between the expected survival and that of the COPD patients reflects the excess mortality due to COPD in these patients.

This paper was also presented as a poster at the European Respiratory Society 2001 Annual Congress in Berlin and at the TSANZ meeting in Cairns 2002.

Cranston, J.M., Nguyen, A.M. and Crockett, A.J. (2004) The relative survival of COPD patients on long-term oxygen therapy in Australia: a comparative study. *Respirology*, v. 9 (2), pp. 237-242, June 2004

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.1111/j.1440-1843.2004.00567.x>

CHAPTER 15

Conclusion

The peer-reviewed published papers presented in this thesis represents the most extensive source of survival and quality of life data for COPD patients on LTOT in Australia. Furthermore, the Health-Related Quality of Life collection of papers represents, according to reviewers comments, "new and original work" and is "one of the few in the world literature to examine HRQoL effects on outcomes rather than the more common approach of using HRQoL as an outcome".

In particular, the published work has generated worldwide interest among researchers and has led to national and international collaborations. The papers have impacted on clinical practice with results being incorporated into a guideline covering home oxygen therapy by the largest Health Maintenance Organisation in the United States as well as the Thoracic Society of Australia and New Zealand's Position paper for LTOT. The results of the reported studies have been used in developing several educational web sites, including the University of Toronto's Discovery Campus Management of COPD web based course. This course provides information for patients, carers and health care professionals. They have also led to the completion of an additional Cochrane Review on the use of domiciliary oxygen therapy in interstitial lung disease. Furthermore they have provided the background for the generation of the hypothesis for the current international randomised control trial of the use of palliative oxygen therapy in patients with dyspnoea who are not hypoxaemic. The results of the latter study will provide evidence

for incorporation into guidelines for the prescription of palliative home oxygen therapy, worldwide.

The work reported has led to the development of innovative strategies to improve the management of care for patients with COPD, This includes the new specialist respiratory nurse practitioner role to provide additional care to COPD patients, and provided detailed information on the development of an Australian guideline for the management of COPD, COPDX.

The published work has led to invitations to a series of meetings with state government authorities to discuss the provision of oxygen therapy in South Australia with particular reference to the provision of oxygen therapy in rural and remote regions. This has led to the development of a specifications for oxygen therapy that will be used by the Department of Health to call tenders for the provision of this service in South Australia The work has also highlighted several important areas for future research within COPD and other chronic lung disease groups where current Australian evidence to support clinical practice is lacking, for example oxygen therapy in interstitial lung disease and palliative care in non- respiratory disease.

Impact of the publication of the results of the longitudinal study

The importance of the results has been recognised by many professional societies and research groups both within Australia and overseas. As a direct result of the dissemination of the results through a detailed report to the NH&MRC and presentations at both national and international scientific meetings, collaborations and sharing of information has occurred between

our Unit and researchers in the United Kingdom (UK), Poland, Norway, New Zealand, Russia, Denmark, United States of America (US) and Canada.

In particular:

The papers have been used in the development of a "Coverage Policy Bulletin" covering oxygen for home use by "Aetna", a leading US health care and related benefits organisation, providing a spectrum of products and services including health care, dental, vision, pharmacy, group life disability and long-term care coverage. Aetna currently serves 17.5 million health care members, 13.7 million dental members and 11.7 million group insurance members. It has an expansive nationwide network of more than 498,000 health care services providers, including over 308,000 primary care and specialist physicians and 3,200 hospitals (167)

As a result of the publications the need to educate general practitioners (GP) in the role of, and benefits to be expected from, LTOT, I was appointed to an Advisory Board, a 6-member group of internationally recognised experts, for the University of Toronto's "Discovery Campus." This distance-learning web-based teaching package was developed in conjunction with respiratory clinicians and researchers from the University of Toronto, Canada. It aims to provide training in the prescription and correct use of oxygen therapy for GPs and other health professionals and to act as an information site for patients and their carers. We specifically adapted this site to make it relevant for use by Australian health professionals, patients and carers. The Australian version is based almost entirely on the results of the previous reported papers and related findings.

The work has been cited in a report on women and smoking by the US Surgeon General 2001 (61) and by Barnes in the *New England Journal of Medicine* (46) Other citations have been made by authors in Norway (168) Chile and Colombia. Our Cochrane Review of domiciliary oxygen for COPD was recently cited by the Cochrane Collaboration Primary Health Care Field, SUNY Upstate Medical University, New York, as being of special relevance to primary care. Other citations of the work have been made by the American Thoracic Society and by the American College of Physicians.

The quality of life study was included in a Rapid Report of key papers during TSANZ Annual Scientific Meeting in March 2001. Prior to the release of our report of the evidence for home oxygen therapy in COPD the TSANZ and the Australian Lung Foundation were reluctant to establish a guideline for chronic respiratory disease.

The Cochrane Collaboration Primary Health Care Field

<http://www.upstate.edu/fmed/cochrane/cochabstracts.shtml>

American Thoracic Society. QOL - Specific diseases COPD.

<http://www.atsqol.org/copd.asp>

ACP Journal Club 2001; 134 (2):

<http://www.acponline.org/journals/acpjic/marapr01/otherarticlesnoted.htm>

Thoracic Society of Australia and New Zealand Annual Scientific Meeting

Rapid Report. March 2001

During the research activities associated with the papers presented in this thesis, I recognised the need to provide additional care. In particular this applied to supportive, educational and psychosocial care to patients with COPD, to enable them to contribute more effectively to managing of their disease. There are currently several studies being developed that aim to build a sustainable framework of health care partnerships that integrates existing health care resources and addresses important patient needs, to create a more effective collaborative self-management. The goals of these proposed studies include improved self-management through the development of care plans for the patient, respiratory nurse practitioners in Primary Care and academic detailing to GPs by DATIS. The latter will help GPs develop new approaches to treatment and support clinical practice change.

Recognition of the value of the work was made recently with an anonymous reviewer rating my research team as the best unit in Australia for applied health economic analysis and chronic respiratory disease.

Recommendations

The accumulated knowledge stemming from this research has led to several recommendations.:

1. That funding, initially for a period of three years, be provided for the establishment of a Primary Care Respiratory Unit for research into the management of chronic lung disease in Primary Care. The Unit would promote:

- Research leading to the establishment of guidelines/pathways.

- Coordination of research projects.
- Dissemination of the results.
- The implementation of change management.
- The clinical and economic evaluation of the change.
- The establishment of a national registry of patients on home oxygen therapy.

2. The gaps identified in our existing knowledge on how best to treat COPD suggest that the following research projects should be funded:

- The development of methods to assist general practitioners in detecting cases of early COPD amongst their patients so that they may offer them intensive smoking cessation therapy.
- The cost-effectiveness of a nurse practitioner in the provision of additional care to patients with COPD.
- A randomised controlled trial of home oxygen therapy in palliative care.
- A study of the ability of patients on home oxygen therapy to drive a motor vehicle.
- A study of the prevalence of COPD in Australia.
- The contribution of environmental factors to the prevalence of COPD in an Australian community.

- A study of portable (liquid oxygen) versus stationary oxygen therapy.
- A study of the cost-effectiveness of policy change concerning the management of COPD.
- A study of the trajectory of end-stage COPD.
- A study of the use of home oxygen therapy in interstitial lung disease.
- Alternative models of the provision of oxygen therapy

The previous body of work presented in this thesis has identified inequalities in the provision of home oxygen therapy in Australia between states and between rural and metropolitan regions within states. This led me to an exploration of alternative models of the provision of oxygen therapy, in particular models in countries where current oxygen registries exist (e.g. France, Poland and Sweden).

An extensive search of the literature identified 6 papers which provided information on the oxygen registers in the European countries of Denmark, France Sweden and Poland (169-174). A site visit to Poland in September 2001 and contacts with key stakeholders in France and Sweden have provided additional information on the nature and functioning of the oxygen registers in these countries.

ANTADIR

In France, home-care for patients with respiratory failure is provided either through a commercial sector or through a non-profit organisation. The national coordinating body ANTADIR (Association Nationale pour le

Traitement A Domicile de l'Insuffisance Respiratoire chronique) was created in 1981 at the request of the then Ministry for Health, and federates the network of SARD (Service d'Assistance Respiratoire à Domicile) regional associations. This non-profit network links a group of 33 regional associations to provide of domiciliary aids and home care of patients with chronic respiratory insufficiency.

As well as federating the Regional associations, ANTADIR evaluates their experiences on a National level and involves representatives from government, funding authorities and scientific societies.

The principal roles of ANTADIR include:

- Coordination of the provision of domiciliary respiratory equipment to patients with diseases requiring such equipment. The diseases treated are predominantly chronic severe lung disease treated with LTOT and assisted ventilation and sleep apnoea syndrome treated with continuous positive airway pressure.
- Overall management of the SARD network of regional associations by medical and technical coordination of these associations and of their medical, technical social and administrative staff.
- Centralisation of equipment purchases such as oxygen concentrators, ventilators, etc.
- Supporting research of a medical, technical and socio-economic nature as well as serving as a National Registry of patients.

- Analysing and disseminating information on respiratory disease.
- Conducting training programs for health professionals.
- Involvement in patient education (manuals and newsletters).
- Providing computer-programming services for regional associations.
- Undertaking National and International collaborations and exchanges.

The principal role of the regional associations is to provide a total patient care management plan. The patients are primarily; adults (chronic respiratory failure, sleep apnoea syndrome), children (cystic fibrosis, neuromuscular disease) and infants (bronchopulmonary dysplasia). The regional associations provide the apparatus and structure to install and maintain this apparatus in the home. The cost of this service to the patient is covered by the French social security system. The GP continues, in parallel, to follow the patient at home, in consultation with the respiratory specialist. The regional associations serve a social non-profit making purpose and are controlled by representatives of the beneficiaries of the services provided.

The roles of the regional associations include:

- Delivery and maintenance of respiratory assistance equipment.
- Supply of disposable equipment.
- Personalised patient education.
- Checks on appropriate use of equipment.

- Monitoring of treatment compliance.
- Feedback to prescribing physicians.
- Patient assistance with daily needs - social security, ventilatory assistance in the home, housing transport holidays etc.

Other European countries maintain national registers of respiratory patients requiring domiciliary therapies. Switzerland includes patients on home oxygen therapy, mechanical ventilation and sleep disorders in a register. Sweden and Poland have national registers for patients receiving domiciliary oxygen therapy (169-174).

Disadvantages of a National register include:

- The costs involved in establishing and maintaining the register.
- Privacy issues.
- Addressing inequalities in the provision of home oxygen therapy

Longitudinal data collection

The database created to facilitate this research represents the most extensive source of survival data for patients on LTOT in Australia.

Throughout my research I have actively engaged with COPD patients which has generated important insights for the future management of this disease and its co-morbidities. The study of the HRQoL of COPD patients on home oxygen therapy highlighted the impact of emotional functioning and living alone on the survival of these chronically ill patients. The clinical

management of COPD has not, in the past, considered the potential role of HRQoL in the disease process. If HRQoL impacts on survival and is a proxy for physical or general health status, then such measures could be used to stratify patients into risk levels, allowing high risk to be responded to more intensively than low risk. If poor HRQoL plays a causal role in increasing mortality, psychosocial interventions aimed at reducing distress may be effective. The impact of HRQoL on survival in COPD warrants further investigation. This is dependent, however, on future funding to further document the patients' clinical, physiological and social measures that predict the trajectory of the course of COPD. Future research should include:

1. The role of a nurse practitioner in the care of patients with COPD

Over recent years, the transition of patients from the home to hospital to home/community care has changed in conjunction with increased pressure on reducing length of hospital stay. Patients are often discharged home immediately after their acute care requirements have been fulfilled. Our previous work on home oxygen therapy and COPD has highlighted a major hiatus between a COPD patient leaving hospital and becoming safely established at home. In particular, COPD patients often present as extremely disabled "respiratory cripples" and may be unable or reluctant to visit their GP for continued care. Some COPD patients also believe that their GP may be unable to provide the complexity of care that they require due to their multiple (average of six) comorbidities.

In other countries, nurse practitioner roles have evolved from the need to provide improved access and affordable quality health care to increasingly

complex patients. Nurse Practitioners (advanced practice nurses) are able to coordinate the patient's care both within and beyond the hospital setting, complementing the current clinical care already provided. They may expand the hospital's ability to respond effectively and efficiently to evolving demands on the health care system. The nurse practitioner may also serve as an additional contact for rural patients improving access and equity of health care to clients in rural regions.

My research has identified a need for a specialist health practitioner with additional skills to those of the current community-based nurses/health care providers. These skills would include enhanced history taking, diagnostic skills and knowledge of the management of patients with chronic respiratory disease. This health care practitioner would provide a liaison between the hospital care and current community-based health-care services.

Throughout the studies we documented the problem of continued smoking by COPD patients even after the commencement of oxygen therapy. There is a need to change clinician behaviour at the bedside to reinforce the importance of smoking cessation amongst clients. In response to this finding, a smoking cessation project, funded by the South Australian Department of Human Services, was undertaken by partner organisations i.e. the FMC, Repatriation General Hospital, and Noarlunga Health Services in collaboration with the Southern Division of General Practice and the Flinders University Department of General Practice. The project aimed to develop systems in hospitals to ensure that the initiation of smoking cessation interventions with clients is an integral part of the practice of hospital medical and nursing staff

in the future. These systems could include nursing protocols where the “forced” abstinence from smoking due to current hospital no-smoking policies is used to facilitate long-term smoking cessation for these patients.

2. Home oxygen therapy in palliative care

Dyspnoea or difficult and distressing breathing is a common symptom in terminal illness. The prevalence varies according to the underlying disease and ranges from approximately 95% in COPD to 40% in stroke victims (175). Breathlessness can lead to severe anxiety and impacts on the quality of life of both patients and carers (176).

Palliative care plays a major role in providing symptom relief, with the management of dyspnoea including both pharmacological and non-pharmacological therapies. In recent years, continuous oxygen therapy has been prescribed as palliative treatment for dyspnoea in both hypoxic and normoxic patients. There is no evidence from RCTs however, to support this treatment in normoxic patients and it is conceivable that it may add to the patient's distress (175). The diseases treated by this therapy include COPD, cancer, heart failure, ILD and neuro-muscular diseases.

My previous research activities presented in this thesis highlighted the lack of Level 1 evidence supporting the use of home oxygen therapy in patients who are not hypoxic. Previous studies of the use of oxygen therapy for dyspnoea in end-stage cancer and chronic heart failure have involved the administration of oxygen for short time periods, 15 minutes or less, in the

laboratory situation. These studies have produced conflicting results. Both oxygen and air at flow rates of 4 litres per minute significantly reduced dyspnoea in patients with advanced cancer after 15 minutes administration (97). In a study of patients with chronic heart failure, increased inspired oxygen concentrations improved exercise performance and modified the ventilatory response (177). However, in another study of ambulatory oxygen during walk tests in patients with chronic heart failure, although arterial oxygen saturation was increased after oxygen administration, no effect on breathlessness or distance walked was observed.

The National Health and Medical Research Council has recently funded a single-blinded randomised placebo-controlled crossover study in collaboration with the Palliative Care Unit at the Repatriation General Hospital, Adelaide, South Australia. I am one of the Chief Investigators. This is a multicentre study with recruitment centres in New South Wales, Victoria, Tasmania, and South Australia. Duke University in North Carolina and Addenbrooke Hospital in the United Kingdom are also participating in this study. End-stage patients with dyspnoea are to be randomised to receive either air through a modified oxygen concentrator and portable "C" size air (21% oxygen) cylinders or low-flow oxygen therapy via a concentrator and portable "C" size cylinders. The majority of patients are expected to be suffering from chronic heart failure or lung cancer.

The intervention will be used in the patient's home as required by the patient. After a seven-day treatment phase, patients will be crossed over to the alternative regime. Dyspnoea and quality of life will be measured by validated

instruments at the beginning of the study, at the time of crossover and at the completion of the study. It is proposed that a cost-consequences analysis of oxygen therapy will be undertaken in relation to: the direct cost of therapy; the symptom improvement; the use of other therapies; and health service utilisation during the study period.

The results of this study would produce a seminal paper of worldwide significance.

3. Prevalence of COPD in Australia

The national burden of the morbidity of chronic lung disease has been recognised by The Australian Institute of Health and Welfare (AIHW). In calculating the combined burden of fatal and non-fatal health outcomes, the disability-adjusted life year (DALY) of major disease groups and injury, COPD was rated the third leading cause of disease burden in Australia behind ischaemic heart disease and stroke. Asthma, a national priority target area, was rated the ninth cause of disease burden. The prevalence data used by the AIHW in the calculation of the DALY was extrapolated from data obtained during a study published in 1990 (69, 178). It is not known how representative this data is of the Australian population. The true incidence and prevalence of COPD in Australia is unknown. It is also unknown if this is changing over time, if the incidence and prevalence of COPD is the same for urban and rural regions and whether there are gender or racial differences in the Australian community. Yet this information is critical for the planning of services and allocation of resources to manage this chronic disease.

While other diseases have shown a decline in mortality over recent years, COPD has been reported to be the only leading cause of death world-wide that is increasing in prevalence (66). In Australia, I was able to demonstrate that age standardised mortality from COPD, although decreasing in males, has been steadily increasing in females with Australian female COPD mortality predicted to overtake male mortality within the next five years(16).

4. The contribution of environmental factors to the prevalence of COPD in an Australian community

The contribution of environmental factors to the incidence and prevalence of COPD in Australia is unknown. A recent article concluded that there was consistent evidence that levels of fine particulate matter in the air are associated with a risk of death from all causes and from cardiovascular and respiratory illnesses(179). Particulate matter comes from a variety of sources e.g. cars, smokestacks and gases such as sulphur dioxide, interacting with other compounds in the air. Fine particles can penetrate deep into the lungs. People most at risk from exposure to fine particles include children, the elderly and those with chronic respiratory disease. It is recommended that a study of the effect of fine particulate material in the atmosphere over southern Adelaide on the prevalence of respiratory admissions to the South Australian Hospitals.

5. A study of the cost-effectiveness of policy change in relation to the management of COPD

Economic analyses estimate the costs and benefits of different treatments on the basis of the available evidence. However, the uptake of the results by

physicians is not generally included in the analyses. Recently a method has been developed to determine the policy cost-effectiveness based on the number of patients per practice targeted by the outcome, the policy cost and the policy benefit. The number of patients targeted by the outcome depends on the prevalence of the condition under study and the length of time over which behaviour is influenced(180).

6. A study of the trajectory of end-stage COPD

It is recommended that further studies of the trajectory of end-stage COPD be undertaken with particular emphasis on the HRQoL parameters that have been demonstrated in our previous work to influence survival. The study would assess whether various social factors including the QoL parameters alter the course of mortality in COPD. The potential role of HRQoL in the disease process, the relationship to demographic and physiological parameters and the effect on the clinical management of COPD would be examined. If psychosocial aspects of HRQoL are found to have a causal role in the trajectory of end-stage COPD a significant change in the clinical management of severe COPD may be required.

As stated earlier, the body of work presented in this thesis has generated worldwide interest among researchers and has led to national and international collaborations.

The results have been used in developing several educational web sites, providing information for patients, carers and health care professionals. The results have been translated to other disease groups with the completion of a Cochrane Review of the use of domiciliary oxygen therapy in interstitial lung

disease and the proposed study of the use of palliative oxygen therapy in patients with dyspnoea who are not hypoxaemic. The results of the latter study would provide evidence for incorporation into guidelines for the prescription of palliative home oxygen therapy worldwide.

The research has led to the development of innovative strategies to improve the management of care for patients with COPD, such as the new specialist respiratory nurse practitioner role to provide additional care to COPD patients and the formation of a working party to develop an Australian guideline for the management of COPD.

The peer-reviewed publications have led to the candidate being invited to a series of meetings with state government authorities to discuss the provision of oxygen therapy in South Australia particularly with reference to the provision of oxygen therapy in rural and remote regions. The overall body of work has highlighted several important areas for future research within both the disease group under study and other disease groups where current evidence to support clinical practice is lacking.

The provision of domiciliary oxygen therapy in Australia represents an enormous challenge for the future in the face of the ever-increasing number of patients requiring this therapy and the many other calls upon the health dollar. To reduce inequalities in the provision of this therapy a collaborative approach is required. A workshop of physicians, nurses, carers and patients around Australia could provide an opportunity to discuss a more systematic approach to the provision of this service. Topics for discussion could include:

- Coordinated data recording with emphasis on monitoring outcomes.

- A revised organisational framework.
- Coordination of existing activities.
- The monitoring of appropriate key performance indicators.
- Promotion of educational and other activities.
- Case finding of early COPD and smoking cessation to prevent progression to the requirement for LTOT.

Future research topics include the more detailed investigation of the observed survival advantage of patients receiving liquid oxygen therapy. This will determine whether it has a role in the provision of care of COPD in Australia.

BIBLIOGRAPHY

1. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease: a clinical trial. *Annals of Internal Medicine* 1980; 93:391-398.
2. Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981; 1:681-686.
3. Kettel LJ, Bigelow DB, Levine BE. Recommendations for continuous oxygen therapy in chronic obstructive lung disease. Report of the committee on Emphysema, American College of Chest Physicians. *Chest* 1973;64:505.
4. Block AJ, Burrows B, Kanner RE, Lilker ES, Mithoefer JC, Petty TL. Oxygen administration at home. *American Review of Respiratory Disease* 1977; 115:897-899.
5. Woolcock AJ. Long-term oxygen therapy in Australia. *Respir Care* 1983;28(7):926-8.
6. Breslin ABX, Colebatch HJH, Engel L, Woolcock AJ. Domiciliary oxygen treatment. *Medical Journal of Australia* 1985; 142(9): 508-510.
7. Crockett AJ. Oxygen concentrators--an economical new technology. *Medical Journal of Australia* 1985; 142(9):512-3.
8. Crockett AJ, Alpers JH, Chalmers JP. Cost centre management: how it helped reduce home oxygen costs. *Australian Health Review* 1986;9(1):38-42.
9. McKeon JL, Saunders NA, Murree-Allen K. Domiciliary oxygen: rationalization of supply in the Hunter region from 1982-1986. *Medical Journal of Australia* 1987; 146(2): 73-8.
10. Crockett A, Moss J, Alpers J. The continuing impact of home oxygen therapy for respiratory patients on a hospital budget. *Australian Health Review* 1992; 15(3): 259-68.
11. Crockett AJ, Cranston JM, Moss JR, Alpers JH. Initial trends in quality of life and survival in CAL patients on domiciliary oxygen therapy. *Monaldi Arch Chest Dis* 1996;51(1):64-71.
12. Crockett AJ, Cranston JM, Moss JR, Alpers JH. Effects of long-term oxygen therapy on quality of life and survival in chronic airflow limitation. *Monaldi Arch Chest Dis* 1999;54(2):193-6.
13. Crockett AJ, Cranston JM, Moss JR, Alpers JH. Survival on long-term oxygen therapy in chronic airflow limitation: from evidence to outcomes in the routine clinical setting. *Intern Med J* 2001;31(8):448-54.
14. Crockett AJ, Alpers JH, Moss JR. Home oxygen therapy: an audit of survival. *Aust N Z J Med* 1991;21(2):217-21.

15. Crockett AJ, Moss JR, Cranston JM, Alpers JH. The effects of home oxygen therapy on hospital admission rates in chronic obstructive airways disease. *Monaldi Arch Chest Dis* 1993;48(5):445-6.
16. Crockett A, Cranston J, Moss J, Alpers J. Trends in chronic obstructive pulmonary disease mortality in Australia. *Medical Journal of Australia* 1994;161:600-603.
17. Crockett AJ, Cranston JM, Moss JR, Alpers JH. The MOS SF-36 health survey questionnaire in severe chronic airflow limitation: comparison with the Nottingham Health Profile. *Qual Life Res* 1996;5(3):330-8.
18. Crockett AJ, Moss JR, Cranston JM, Alpers JH. Home oxygen therapy in Australia. *Monaldi Arch Chest Dis* 1996;51(5):444-5.
19. Crockett AJ, Cranston JM. Nonconventional indications of long-term oxygen therapy: oxygen therapy during exercise. *Monaldi Arch Chest Dis* 1999;54(1):72-4.
20. Crockett AJ, Cranston JM, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2000(4):CD001744.
21. Crockett A, Cranston J, Moss J, Scown P, Mooney G, Alpers J. Program budgeting and marginal analysis: a case study in chronic airflow limitation. *Aust Health Rev* 1999;22(3):65-77.
22. Crockett AJ, Moss JR, Cranston JM, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2000(2):CD001744.
23. Crockett AJ, Cranston JM, Moss JR, Alpers JH. A review of long-term oxygen therapy for chronic obstructive pulmonary disease. *Respir Med* 2001;95(6):437-43.
24. Crockett AJ, Cranston JM, Moss JR, Alpers JH. The impact of anxiety, depression and living alone in chronic obstructive pulmonary disease. *Qual Life Res* 2002;11(4):309-16.
25. Cranston JM, Nguyen AM, Crockett AJ. The relative survival of COPD patients on long-term oxygen therapy in Australia: A comparative study. *Respirology* 2004;9(2):237-42.
26. Sullivan SD, Buist AS, Weiss K. Health outcomes assessment and economic evaluation in COPD: challenges and opportunities. *European Respiratory Journal* 2003;21(Supplement 21):1s - 3s.
27. Gulsvik A. The global burden and impact of chronic obstructive pulmonary disease worldwide. *Monaldi Archives of Chest Disease* 2001;56:261 -264.
28. Wedzicha JA. Exacerbations: Etiology and Pathophysiologic Mechanisms. *Chest* 2002;121(5):136S-141S.
29. Comroe J, Jr., Drips R. *The Physiological Basis for Oxygen Therapy*. First ed. Springfield, Illinois, USA.: Charles C Thomas; 1950.
30. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global*

Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001;46(8):798-825.

31. Lundback B, Lindberg A, Lindstrom M, Ronmark E, Jonsson AC, Jonsson E, et al. Not 15 but 50% of smokers develop COPD?--Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir Med* 2003;97(2):115-22.
32. Hogg J. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004;364:709-721.
33. Glanze W, Anderson K, Anderson L. *Mosby's medical and nursing dictionary*. Second ed. St Louis, Missouri: C.V. Mosby Company; 1986.
34. Badham C. *An essay on bronchiolitis: with a supplement containing remarks on simple pulmonary abscess*. 2nd ed. London, England.: J Callow; 1814.
35. Laennec RTH. *A treatise on the diameter of the chest and mediate auscultation*. 2nd ed. London, England.: TG Underwood; 1827.
36. Hutchinson J. On the capacity of the lungs, and on the respiratory movements, with a view of establishing a precise and easy method of detecting disease by the spirometer. *Med Chir Tr* 1846;29:137-161.
37. Christie RV. Emphysema of the lungs (part II). *British Medical Journal* 1944;1-145.
38. Oswald NC, Harold JT, Martin CJ. Clinical patterns of chronic bronchitis. *Lancet* 1953;2:639-643.
39. Ciba Guest Symposium. Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions. *Thorax* 1959;14:286-299.
40. Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases ATS. Definitions and classification of chronic bronchitis, asthma, and pulmonary emphysema. *American Review of Respiratory Disease* 1962;85:762-769.
41. Burrows B, Fletcher CM, Heard BE, et al. The emphysematous and bronchial types of chronic airway obstruction: a clinopathological study of patients in London and Chicago. *Lancet* 1966;1:830-835.
42. Hogg JC, Macklem PT, Thurlbeck WMT. Site and nature of airway obstruction in chronic obstructive pulmonary disease. *New England Journal of Medicine* 1968;278:1355-1360.
43. Rubinfeld AR, Pain MCF. Respiratory Disability in worker's compensation claimants. *Medical Journal of Australia* 1983;1:119-121.
44. Thurlbeck WMT. Changes in lung structure. In: Macklem P, Permutt S, editors. *The lung in transition between Health and Disease*. New York and Basel.: Marcel Dekker; 1979.
45. Barnes PJ. Mechanisms of COPD:differences from asthma. *Chest* 2000;117:10S-14S.
46. Barnes PJ. Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine* 2000;343:269-280.
47. Barnes PJ. Small Airways in COPD. *New England Journal of Medicine* 2004;350(26):2635-2637.

48. Jeffrey PK. Structural and inflammatory changes on COPD: a comparison with asthma. *Thorax* 1998;53.
49. Vikgren J, Friman O, Borga M, Boijesen M, Gustavsson S, Ekberg-Jansson A, et al. Detection of mild emphysema by computed tomography density measurements. *Acta Radiol* 2005;46(3):237-45.
50. Corless J. The aetiology and epidemiology of chronic obstructive pulmonary disease. Malden: Blackwell Publishing; 2003.
51. Petty TL. COPD in perspective. *Chest* 2002;121(5 Suppl):116S-120S.
52. Petty TL, Silvers GW, Stanford RE. The morphology and morphometry of small airways disease(relevance to chronic obstructive pulmonary disease). *Transactions of the American Clinical Climatological Association* 1982;94:130-140.
53. Burrows B, Knudson RJ, Camilli AE, Lyle SK, Lebowitz MD. The "Horse-Racing Effect" and Predicting Decline in Forced Expiratory Volume in One Second from Screening Spirometry. *American Review of Respiratory Disease* 1987;135:788-793.
54. Hensley MJ, Saunders NA. Clinical epidemiology of chronic obstructive pulmonary disease. 1st ed. New York: Marcel Dekker,Inc.; 1989.
55. Kinsman RA, Yaroush RA, Fenandez E, Dirks JF, Schocket M, Fukuhara J. Symptoms and experiences in chronic bronchitis and emphysema. *Chest* 1983;83. 755-761.
56. Fletcher EC, Martin RJ. Sexual dysfunction and erectile impotence in chronic obstructive pulmonary disease. *Chest* 1982;81:413-421.
57. Huppert F. Memory impairment associated with chronic hypoxia. *Thorax* 1982;37:858-860.
58. Sykes MK, McNicol MW, Campbell EJM. *Respiratory Failure*. Philadelphia,PA: Blackwell Scientific Publications; 1969.
59. Australian Bureau of Statistics. 1995 National Health Survey: Asthma and other Respiratory Conditions. Canberra: ABS; 1997. Report No.: Cat No. 4373.0.
60. Australian Institute of Health and Welfare. Personal communication. In: Crockett A, editor. Canberra; 1999.
61. US Department of Health and Human Services. *Women and Smoking*. Washington: United States. Public Health Service. Office of the Surgeon General; 2001. Report No.: NNBCWV.
62. Wilson D, Ruffin R, Grande ED, Smith B, Southcott AM. COPD prevalence in South Australia. *American Journal of Respiratory & Critical Care Medicine* 2002;165(8):A558.
63. Abramson M, Matheson M, Wharton C, Sim M, Walters EH. Prevalence of respiratory symptoms related to chronic obstructive pulmonary disease and asthma among middle aged and older adults. *Respirology* 2002;7(4):325-31.
64. Abramson M, Matheson M, Wharton C, Walters EH. Prevalence of asthma and chronic obstructive pulmonary disease in middle aged and older adults. *Respirology* 2003;8(S):A59.

65. Tan WC, Seale JP, Charaoenratanakaul S. Chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine* 2001;163(5):A81.
66. Hurd S. The impact of COPD on lung health worldwide: epidemiology and incidence. *Chest* 2000;117(2 Supplement):1S-4S.
67. Mathers C, Vos T, Stevenson C. The Burden of Disease and Injury in Australia. Canberra, A.C.T.: Australian Institute of Health and Welfare; 1999. Report No.: AIHW Cat No PHE-17.
68. Regional COPD Working Group. COPD prevalence in 12 Asia-Pacific countries and regions: Projections based on the COPD prevalence estimation model. *Respirology* 2003;8:192-198.
69. Peat JK, Woolcock AJ, Cullen K. Decline of lung function and development of chronic airflow limitation: a longitudinal study of non-smokers and smokers in Busselton, Western Australia. *Thorax* 1990;45(1):32-7.
70. Maguire G, McDonald S, Bengner N, Currie B. The under-recognition of chronic respiratory disease in a remote indigenous Australian community. *Respirology* 2003;8(S):A59.
71. Cunningham J, Sibthorpe B, Anderson I. Occasional paper: Cigarette smoking among indigenous Australians. Canberra: Australian Bureau of Statistics; 1997. Report No.: ABS Cat No 4701.0.
72. Australian Bureau of Statistics. Deaths, Australia. Canberra: Cat.No. 3302.0; 2001.
73. Australian Institute of Health and Welfare. National hospital morbidity data 1997-98 to 2000-01. In. <http://www.aihw.gov.au/dataonline/index.html> (2nd August).
74. Strassels S, Smith D, Sullivan S, Mahajan P. The costs of treating COPD in the United States. *Chest* 2001;119(2):344-352.
75. Mathers C, Penm R, Carter R, Stevenson C. Health system costs of diseases and injury in Australia 1993-94. Canberra: Australian Institute of Health and Welfare; 1998. Report No.: Series 2.
76. Mathers C, Stevenson C, Carter R, Penm R. Diseases costing methodology used in the Disease Costs and Impact Study 1993-94. Canberra: Australian Institute of Health and Welfare; 1998. Report No.: AIHW Cat No HWE 7.
77. Health Insurance Commission. HIC Annual report 2000-01. In: hic. http://www.hic.gov.au/statistics/dyn_mbs/forms/mbsgtab4.html (2nd August).
78. Australian Institute of Health and Welfare. Australia's Health 2000. Canberra: AIHW; 2001. Report No.: Cat. No. AUS-19.
79. Australian Institute of Health and Welfare. Chronic diseases and associated risk factors in Australia, 2001. Canberra: Australian Institute of Health and Welfare; 2001. Report No.: Cat. No. PHE 33.
80. Australian Institute of Health and Welfare. Hospital statistics 2000-01. Canberra: AIHW; 2002. Report No.: Cat. No.HSE-20.

81. Frith P. Case Statement:Chronic Obstructive Pulmonary Disease. Brisbane: Australian Lung Foudation; 2001.
82. Leigh J, Romano P, Schenker M, Kreiss K. Costs of occupational COPD and Asthma. *Chest* 2002;121(1):264-272.
83. Sullivan S, Ramsey S, Lee T. The economic burden of COPD. *Chest* 2000;117(2 Suppl.):5s-9s.
84. Streeton JA. Long term oxygen therapy in Australia. In: Crockett AJ, editor. East Melbourne; 2004.
85. Astrup P, Severinghaus J. The History of Blood Gases, Acids and Bases. 1st ed. Copenhagen: Radiometer A/S; 1986.
86. Earnest MA. Holding your breath: The lived experience of Supplemental Oxygen Therapy [PhD]. Denver: University of Colorado; 2001.
87. Leigh JM. Early treatment with oxygen. The Pneumatic Institute and the panaceal literature of the nineteenth century. *Anaesthesia* 1974;29(2):194-208.
88. Martin L. Oxygen Therapy: The First 150 Years. In: Mt Sinai Medical Centre. n.d. January 1999. <http://www.mtsinai.org/pulmonary/papers/ox-hist/ox-hist-intro.html> (4 October 2001).
89. Birch S. On Oxygen as a Therapeutic Agent. *British Medical Journal* 1859(CLVII):1053-1055.
90. Leigh JM. Ideas and anomalies in the evolution of modern oxygen therapy. *Anaesthesia* 1974;29(3):335-48.
91. Campbell EJM. Methods of oxygen administration in respiratory failure. *Annals of the New York Academy of Science* 1965;121:861.
92. Tjep BL. Portable Oxygen Therapy: including oxygen conserving methodology. New York: Futura Publishing Company,Inc.; 1991.
93. Petty TL, Finigan MM. Clinical evaluation of prolonged ambulatory oxygen therapy in chronic airway obstruction. *American Journal of Medicine* 1968;45:242.
94. Barach A. The therapeutic use of oxygen. *Journal of the American Medical Association* 1922;79(9):693-699.
95. Meltzer SJ. Therapeutic value of oral rhythmic insufflation of oxygen. *Journal of American Medical Association* 1917;69:1150.
96. Douglas CG. Discussion on therapeutic uses of oxygen. *Proceedings of the Royal Society of Medicine* 1920;13:59.
97. Booth S, Kelly MJ, Cox NP, Adams L, Guz A, 1515-8 AJRCCM. Does oxygen help dyspnea in patients with cancer? *American Journal of Respiratory & Critical Care Medicine* 1996;153(5):1515-1518.
98. Cotes J, Gilson J. Effect of oxygen on exercise ability in chronic respiratory insufficiency. *Lancet* 1956;i:872-876.
99. Barach AL. Ambulatory Oxygen Therapy: Oxygen Inhalation at Home and Out-of-Doors. *Diseases of the Chest* 1959;35(3):229-241.
100. Campbell EJ. Oxygen Administration. *Anaesthesia* 1963;18:503-6.

101. Campbell EJM. Oxygen therapy in diseases of the chest. *British Journal of Diseases of the Chest* 1964;58:1459-159.
102. Sackner MA. A history of oxygen use in chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 1974;110:25-34.
103. Levine BE, Bigelow DB, Hamstra RD, Beckwitt HJ, Mitchell RS, Nett LM, et al. The Role of Long-term Continuous Oxygen Administration in Patients with Chronic Airway Obstruction with Hypoxemia. *Annals of Internal Medicine* 1967;66(4):639-650.
104. Petty TL. Historical perspectives on long term oxygen therapy. In: O'Donohue WJ, editor. *Long Term Oxygen Therapy, Scientific Basis and Clinical Application*. 81 ed. New York: Marcel Dekker Inc.; 1995. p. 1 - 20.
105. Gorecka A, Gorzelak K, Sliwinski P, Tobiasz M, Zielinski J. Effects of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997;52:674-679.
106. Strom K, Boe J, Boman G, Midgren B, Rosenhall L. Long-term domiciliary oxygen therapy. *Monaldi Archives of Chest Disease* 1993;48:473-478.
107. Strom K, Boe J. Quality assessment and predictors of survival in long-term domiciliary oxygen therapy. *European Respiratory Journal* 1991;4:50-58.
108. Dubois P, Jamart J, Machiels J, Smeets F, Lulling J. Prognosis of severely hypoxemic patients receiving long-term oxygen therapy. *Chest* 1994;105(2):469-474.
109. Ringbaek TJ, Lange P. The impact of the Danish Oxygen Register on adherence to guidelines for long-term oxygen therapy in COPD patients. *Respir Med* 2005.
110. Roselle S, D'Amico F. The effect of home oxygen therapy on hospital admission rates of patients with COPD. *Respiratory Care* 1990;35:213.
111. Young IH, Crockett AJ, McDonald CF. Adult domiciliary oxygen therapy. Position statement of the Thoracic Society of Australia and New Zealand. *Med J Aust* 1998;168(1):21-5.
112. Charles C. South Australian Health Commission Administrative Circular. 1998;1.33(3).
113. Walshaw MJ, Lim R, Evans CC, Hind CRK. Prescription of oxygen concentrators for long-term oxygen treatment: reassessment in one district. *British Medical Journal* 1988;297:1030-1032.
114. Stewart AG, Howard P. Indications for long-term oxygen therapy. *Respiration* 1992;59 Suppl 2:8-13.
115. McSweeney AJ, Grant I, Heaton RK. Life quality of patients with chronic obstructive pulmonary disease. *Archives of Internal Medicine* 1982;142:473 - 478.
116. Kaptein AA, Brand PL, Dekker FW, Kerstjens HA, Postma DS, Sluiter HJ. Quality-of-life in a long-term multicentre trial in chronic nonspecific lung disease: assessment at baseline. The Dutch CNSLD Study Group. *European Respiratory Journal* 1993;6(10):1479-84.
117. Neff TA, Petty TL. Outpatient care for patients with chronic airway obstruction: emphysema and bronchitis. *Chest* 1971;Supplement:11s-17s.

118. Morgan AD, Peck DF, Buchanan DR, McHardy GJ. Effect of attitudes and beliefs on exercise tolerance in chronic bronchitis. *British Medical Journal* 1983;286:171-173.
119. Burns BH, Howell JBL. Disproportionately severe breathlessness in chronic bronchitis. *Quarterly Journal of Medicine* 1969;38:277-294.
120. Phillips GD, Harrison NK, Cummin ARC, Ward J, Shenoy VS, Newey V, et al. A new method for measuring compliance with long-term oxygen treatment. *British Medical Journal* 1994;308:1554-1555.
121. Fletcher EC, Luckett RA, Goodnight-White S, Miller CC, Qian W, Costarangos-Galarza C. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO₂ above 60 mm Hg. *Am Rev Respir Dis* 1992;145(5):1070-6.
122. Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Enrhart M, Schott R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. *Eur Respir J* 1999;14(5):1002-8.
123. Patrick D, Erickson P. *Health Status and Health Policy: Quality of Life in Health Care Evaluation and Resource Allocation*. New York, Oxford.: Oxford University Press; 1993.
124. Petty TL, Bliss PL. Ambulatory Oxygen Therapy, Exercise, and Survival with Advanced Chronic Obstructive Pulmonary Disease(The Nocturnal Oxygen Therapy Trial Revisited). *Respiratory Care* 2000;45(2):204-213.
125. Williams SJ. *Chronic respiratory illness*. London and New York: Routledge; 1993.
126. Dubos R. The state of health and the quality of life. *Western Journal of Medicine* 1976;125(1):8-9.
127. Dudley DL. Coping with chronic COPD: therapeutic options. *Geriatrics* 1981;36(11):69-74.
128. Dudley DL, Glaser EM, Jorgenson BN, Logan DL. Psychosocial concomitants to rehabilitation in chronic obstructive pulmonary disease. Part 2. Psychosocial treatment. *Chest* 1980;77(4):544-51.
129. Dudley DL, Verhey JW, Masuda M, Martin CJ, Holmes TH. Long-term adjustment, prognosis, and death in irreversible diffuse obstructive pulmonary syndromes. *Psychosom Med* 1969;31(4):310-25.
130. Dudley DL, Wermuth C, Hague W. Psychosocial aspects of care in the chronic obstructive pulmonary disease patient. *Heart Lung* 1973;2(3):389-93.
131. Fishman DB, Petty TL. Physical, symptomatic and psychological improvement in patients receiving comprehensive care for chronic airway obstruction. *J Chronic Dis* 1971;24(12):775-85.
132. Brown JS, Rawlinson ME, Hilles NC. Life satisfaction and chronic disease:exploration of theoretic model. *Medical Care* 1981;11:1136-46.
133. Prigatano GP, Wright EC, Levin D. Quality of life and its predictors in patients with mild hypoxaemia and chronic obstructive pulmonary disease. *Archives of Internal Medicine* 1984;144:1913-1919.

134. Hanson EI. Effects of chronic lung disease on life in general and sexuality: Perceptions of adult patients. *Heart & Lung* 1982;11:435-441.
135. Sexton DL, Monro BH. Living with chronic illness: The experience of woman with chronic obstructive pulmonary disease (COPD). *Western Journal Nursing Research* 1988;10:26-44.
136. Yellowlees P, Alpers J, Bowden J, Bryant G, Ruffin RE. Psychiatric morbidity in patients with chronic airflow obstruction. *Medical Journal of Australia* 1987;146:305-307.
137. Janssens JP, Rochat T, Frey JG, Dousse N, Pichard C, Tschopp JM. Health-related quality of life in patients under long-term oxygen therapy: a home-based descriptive study. *Respir Med* 1997;91(10):592-602.
138. Jenkins CD. Assessment of outcomes of health intervention. *Social Science Medicine* 1992;35(4):367-375.
139. Bergner M, Rothman M. Health status measures: An overview and guide for selection. *Annual Review of Public Health* 1987;8:191-210.
140. Williams TF. Geriatrics: A Perspective on Quality of Life and Care for Older People. In: Spilker B, editor. *Quality of Life Assessments in Clinical Trials*. New York: Raven Press Ltd.; 1990. p. 217-223.
141. Engstrom CP, Persson LO, Larsson S, Sullivan M. Health-related quality of life in COPD: why both disease-specific and generic measures should be used. *European Respiratory Journal* 2001;18:69-76.
142. Ware J, Sherbourne C. The MOS 36-item short-form health survey. 1. Conceptual framework and item selection. *Medical Care* 1992;30:473-483.
143. Ware J, Kosinski M, Keller S. *SF-36 physical and mental health summary scales: a user's manual*. Boston, MA.: The Health Institute; 1994.
144. Guyatt G, Berman L, Townsend M, Pugsley S, Chambers L. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773-778.
145. Guyatt G. Measuring health status in chronic airflow limitation. *European Respiratory Journal* 1988;1(6):560-564.
146. Harper R, Brazier JE, Waterhouse JC, Walters SJ, Jones NM, Howard P. Comparison of outcome measures for patients with chronic obstructive pulmonary disease (COPD) in an outpatient setting. *Thorax* 1997;52(10):879-87.
147. Adams DL. Analysis of a life satisfaction index. *Journal of Gerontology* 1969;24(4):470-4.
148. Hunt S, McEwen J, McKenna S. *Measuring Health Status*. Beckenham, Kent: Croom Helm; 1986.
149. Kind P, Carr-Hill R. The Nottingham Health Profile: a useful tool for epidemiologists. *Social Science Medicine* 1987;25:905-910.
150. Viramontes J, O'Brien B. Relationship between symptoms and health-related quality of life in chronic lung disease. *Journal of General Internal Medicine* 1994;9:46-48.

151. Brazier J, Harper R, Jones N, O'Cathain A, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: a new outcome measurer for primary care. *British Medical Journal* 1992;305:160-164.
152. Guyatt G, Juniper E, Walter S, Griffith L, Goldstein R. Interpreting treatment effects in randomised trials. *British Medical Journal* 1998;316:690-693.
153. Donaldson C, Atkinson A, Bond J. Should QALYS be programme -specific? *Journal of Health Economics* 1988;7:239-257.
154. Kalucy L, Marion ,Brighton and Glenelg community health needs assessment: older persons report. Adelaide: South Australian Health Commission; 1989.
155. Behavioural Epidemiology Unit. South Australian population norms for Short Form 36 (SF36) Health Status Questionnaire. Adelaide: South Australian Health Commission; 1995.
156. Christie D. Australian bronchitis mortality. *Medical Journal of Australia* 1971;1:21-25.
157. O'Donohue WJ. Long-Term Oxygen Therapy: Scientific Basis and Clinical Application. 1st ed. New York.: Marcel Dekker,Inc.; 1995.
158. Jones PW. Quality of life: specific problems associated with hypoxaemia. *Monaldi Archives for Chest Disease* 1993;48(5):565-573.
159. Chailleux E, Fauroux B, Binet F, Dautzenberg B, Polu JM. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. A 10-year analysis of ANTADIR Observatory [see comments]. *Chest* 1996;109(3):741-749.
160. Miyamoto K, Aida A, Nishimura M, Aiba M, Kira S, Kawakami Y. Gender effects on prognosis of patients receiving long-term oxygen therapy. The Respiratory Failure Research Group in Japan. *American Review of Respiratory and Critical Care Medicine* 1995;152:972-976.
161. Alonso J, Anto JM, Gonzalez M, Fiz JA, Izquierdo J, Morera J. Measurement of general health status of non-oxygen-dependent chronic obstructive pulmonary disease patients. *Medical Care* 1992;30(5 Suppl):MS125-35.
162. Mahler DA, Mackowiak JI. Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with COPD. *Chest* 1995;107(6):1585-9.
163. McCullum J, Shadbolt B, Wang D. Self-rated health and survival: A 7-year follow-up study of Australian elderly. *American Journal of Public Health* 1994;84:1100-1105.
164. Lynn J, Ely EW, Zhong Z, et al. Living and dying with chronic obstructive pulmonary disease. *Journal of Ameerican Geriatric Society* 2000;48(Suppl,5.):S91-S100.
165. Hakulinen T, Tenkanen L, Abeywickrama K, Paivarinta L. Testing equality of relative survival patterns based on aggregated data. *Biometrics* 1987;43:313-325.
166. Foucher P, Baudouin N, Merati M, Pitard A, Bonniaud P, Reybet-Degat O, et al. Relative survival analysis of 252 patients with COPD receiving long- term oxygen therapy. *Chest* 1998;113(6):1580-1587.

167. Aetna US. Oxygen for home use. In: Aetna U.S. Healthcare. January 7, 2005. <http://www.aetna.com/cpb/data/CPBA002.html> (18 May, 2005).
168. Omenaas E. Handtering av kronisk obstruktiv lungesykdom. Tidsskr Nor Laegeforen 2000;120:550.
169. Ludot A, d'Orbecastel OR. Home respiratory care. Therapie 2001;56(2):143-149.
170. Fauroux B, Howard P, Muir JF. Home treatment for chronic respiratory insufficiency: the situation in Europe in 1992. European Respiratory Journal 1994;7(9):1721-1726.
171. Muir JF, Voisin C, Ludot A. Organization of home respiratory care: the experience in France with ANTADIR. Monaldi Archives for Chest Disease 1993;48(5):462-467.
172. Ringbaek TJ, Lange P, Viskum K. Are patients on long-term oxygen therapy followed up properly? Data from the Danish Oxygen Register. J Intern Med 2001;250(2):131-6.
173. Strom K, Boe J, Boman G, Midgren B, Ropsenhall L. Long-term domiciliary oxygen therapy. Experiences acquired from the Swedish oxygen register. Monaldi Archives for Chest Disease 1993;48:473-478.
174. Zielinski J, Sliwinski P, Tobiasz M, Gorecka D. long-term oxygen therapy in Poland. Monaldi Archives for Chest Disease 1993;48(5):479-480.
175. Zeppetella G. The palliation of dyspnea in terminal disease. American Journal Hospital Palliative Care 1998;15(6):322-330.
176. Luce JM, Luce JA, 1331-7 J. Perspectives on care at the close of life. Management of dyspnea in patients with far-advanced lung disease: "once I lose it, it's kind of hard to catch it..." Journal of the American Medical Association 2001;285(10):1331-1337.
177. Moore DP, Weston AR, Hughes JM, Oakley CM, Cleland JG. Effects of increased inspired oxygen concentrations on exercise performance in chronic heart failure. Lancet 1992;339(8797):850-853.
178. Australian Institute of Health and Welfare. The Burden of Disease and Injury in Australia. Canberra: Australian Institute of Health and Welfare. Report No.: Cat. No. PHE-17.
179. Samet JM, Dominici F, Curriero FC, ., Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. New England Journal of Medicine 2000;343(24):1742-1749.
180. Mason J, Freemantle N, Nazareth I, Eccles M, Haines A, Drummond MJ-. When is it cost-effective to change the behavior of health professionals? Jopurnal of the American Medical Association 2001;286(23):2988 - 2992.

APPENDICIES

Examples of Citations

The Cochrane Review and the Respiratory Medicine paper have been translated into several languages. Also included are examples of citations in other professionals work and international guidelines.

Madsen FF, Jensen LB Langtids oxygenterapi (LTOT) ved kronisk obstruktiv lungesygdom (KOL). Ugeskr Laeger 2001; 20: 2763-6

Crockett AJ, Cranston JM, Moss JR, Alpers JH Ossigenoterapia domiciliare nella broncopneumopatia cronica ostruttiva (Revisione Cochrane)

Crockett AJ, Moss JR, Cranston JM, Alpers, JH. Domiciliary oxygen for chronic obstructive lung disease. (Cochrane Review). Ugeskr Læger 1998; 160: 7135-8.

Crockett AJ, Moss JR, Cranston JM, Alpers JH. Ambulant oksygenbehandling ved kronisk obstruktiv lungesykdom

<http://www.doktoronline.no/pub/mediweb/cochrane/31122180.html>

The peer-reviewed papers have also been cited in the following:

Alvear Téllez, Gonzalo. EPOC. Gui'as Clinical 2001; 1 (9)

Andersson I, Johansson K, Larsson S, Pehrsson K. Long-term oxygen therapy and quality of life in elderly patients hospitalised due to severe exacerbation of COPD. A 1 year follow-up study. Respir Med. 2002 Nov;96(11):944-9.

Barnes PJ Therapy of chronic obstructive pulmonary disease. Pharmacol Ther. 2003 Jan;97(1):87-94.

Barnes PJ. Modern Management of COPD in the Elderly. *Annals of Long-Term Care: Clinical Care and Aging*. 2001; 9[5]:51-56.

Barnes PJ letter N Engl J Med 2000; 343:1971

BMJ Clinical Evidence 2002; Vol. 7 Respiratory disorders. BMJ Publishing Group 2002.

The Boehringer Ingelheim COPD Communication Award Eloquentium

2002 http://www.eloquium.org/download/2002_copd.pdf

Chitkara RK, Sarinas PS. Recent advances in diagnosis and management of chronic bronchitis and emphysema. *Curr Opin Pulm Med*. 2002 Mar;8(2):126-36. Review.

de Dios MS, Calero PS, Olmedo PJM, Caro AJM, Rodrihuez MG, Aliseda AC. EPOC en atencion primaria. Guia de practica clinica basada en la evidence.

SAMFYC, Granada Spain. 2002

European network of COPD associations. European COPD patient manifesto: A vision for change. The Nordic Heart and Lung Association, Brussels Belgium

Kertzjens H, Postma D. Pneumologia: Broncopneumopatia cronica ostruttiva Aggiornato a giugno 2001 Clinical evidence Edizione Italiana numero 2, 2001

<http://www.clinev.it/s012/c048/i293.htm+crockett+aj+and+cranston+jm&hl=en&ie=UTF-8>

Khot A, Polmear A. Practical General Practice: Guidelines for effective clinical management. Chapter 6 Butterworth Heinemann; 1999

Link N, Tanner M. The Bellevue Guide to Outpatient Medicine. An evidence based guide to primary care. Chapter 5; Asthma and chronic obstructive pulmonary disease. [BMJ Books 2001](#)

Madsen F. Korrespondancer [Tobaksrygning og langtidsoxygenterapi. Indikationer og kontraindikationer](#) Ugeskrift for Læger 2002; 8

Magnussen H, Goeckenjan G, Kohler D, Matthys H, Morr H, Worth H, Wuthe H

Guidelines to Long-Term Oxygen Therapy. Pneumologie 2001; 55: 454-464

Network Europeo delle Associazioni dei Pazienti con BPCO Notiziario dell'Associazione Italiana Pazienti BPCO Sensibilizzare l'opinione pubblica sulla BroncoPneumopatia Cronica Ostruttiva (BPCO), le sue cause, i suoi sintomi e la sua natura progressiva è il compito fondamentale del. Focus broncopneumopatia cronica ostruttiva 2002; 3 November:1-6

Omenaas E. Håndtering av kronisk obstruktiv lungesykdom *Tidsskr Nor Lægeforen* 2000; 120: 550.

Sanders MH, Newman AB, Haggerty CL, Redline S, Lebowitz M, Samet J, O'Connor GT, Punjabi NM, Shahar E; Sleep Heart Health Study. Sleep and

sleep-disordered breathing in adults with predominantly mild obstructive airway disease. Am J Respir Crit Care Med. 2003 Jan 1;167(1):7-14.

Schulmeister L. Am J Nursing 2001: 101(10); 15 letter

O₂ Rreport -ausgabe. Die Lungentransplantation im Brennpunkt Erfolgreicher Patientenkongress für Sauerstoff-Langzeit-Therapie in Bad Reichenhall No 1. 2002 http://212.227.33.34/bundesverband/politik/download/dmp_copd.pdf

St. Franziskus Hospital Köln Therapie bei Disease Management für Chronisch obstruktive Lungenerkrankung Arbeitsgruppe Praktische Evidenz-basierte Medizin"

Авдеев СН, Царева НА, Чучалин АГ, НИИ пульмонологии МЗ РФ, Москва Лечение легочной гипертензии при хронической обструктивной болезни легких. www.ossn.ru/jsn/n3/144.htm

Wilkens H, Sybrecht GW. [COPD: stage-appropriate therapy] Internist (Berl). 2001 Dec;42(12):1651-64.

This published work has been incorporated into guidelines

Australia

Department of Human Services South Australia. Domiciliary oxygen guidelines. October 2002

North Western Health. Victoria. Royal Melbourne Hospital. Evidence based guidelines. Hospital management of an acute exacerbation of chronic obstructive pulmonary disease. October 1999

North Western Health. Victoria. Western Hospital. Evidence based guidelines. Hospital management of an acute exacerbation of chronic obstructive pulmonary disease. October 1999

USA

Aetna: Coverage Policy Bulletins Number: 0002 Subject: Oxygen for Home Use May 31, 2002

Italy

Guidelines for the diagnosis and management of COPD.

http://www.asl1.umbria.it/first_page/linee_guida/bpco/introduzione.htm

http://www.asl1.umbria.it/first_page/linee_guida/bpco/biblio.htm

Denmark

Used in developing a guideline for the prescription of oxygen therapy in Denmark.

Other Websites, information sites and reports

Alvear Tellez Gonzalo Fisterra.com EPOC 4 Nov 2000

<http://www.apred.info/ar/pdf/epoc.pdf>

EBOC Evidence based on call data

basehttp://www.eboncall.co.uk/CATs/COPD_Crockett_00.htm

Emphysem-info Aktuelle Informationen zum Thema "Emphysem" July 2001.

<http://www.emphysem-info.de/aktuell/010726.htm>

Fisionet. [A Fisioterapia na Internet](#) A Brazilian information web site for health professionals. <http://www.fisionet.com.br/abstracts.asp>

Healthinfo4u A health information site for patients. Lung disorders

http://www.healthinfo4u.org/results_pages/Lung_Disorders-2.html

HEXAL ARGENTINA S.A Informes EBOC: Enfermedad Broncopulmonar

Obstructiva Crónica <http://www.hexal.com.ar/libroeboc/libroeboc4.10.1.htm>

Jefferson T. Health Reviews Ltd and UK Cochrane Centre for Dr Robert Scherpier on behalf of Strategy Development and Monitoring for Endemic Bacterial and Viral Diseases, Communicable Disease Control Prevention and Eradication, World Health Organization, Geneva. The evidence base to treatment in the guide for the treatment of patients presenting respiratory symptoms at the primary level of health services (health posts)

Jefferson T Health Reviews Ltd and UK Cochrane Centre for Dr Robert Scherpier on behalf of Strategy Development and Monitoring for Endemic Bacterial and Viral Diseases, Communicable Disease Control Prevention and

Eradication, World Health Organization, Geneva. The evidence base to treatment in the guide for the treatment of respiratory diseases at district level

Mt Sinai School of Medicine. New York Scientifically sound studies for geriatrics 1997-2000

<http://www.mssm.edu/geriatrics/education/ebm/bibliography/bibliography.pdf>

National Respiratory Training Centre provides accredited education and training in respiratory and allergic disease for health professionals.

<http://www.sussex.ac.uk/tcmr/pgp/pgp2/pgp2/respiratory.html#COPD>

Nordic Heart and Lung Association. European COPD patient manifesto: A vision for change. <http://www.efanet.org/imgs/pdf/manifesto-eng.pdf>

Notiziario dell'Associazione Italiana Pazienti. Focus BPCO broncopneumopatia cronica ostruttiva November Number 3 2002

www.efanet.org/imgs/pdf/manifesto-ita.pdf

Petty T. Chronic obstructive pulmonary disease. Best Practice of Medicine, Pulmonary and critical care medicine. July 2001.

<http://merck.praxis.md/common/bpm/bpm.asp?page=BPM01PU01>

Pharmacists COPD accreditation website. [Pfizer Canada Boehringer Ingelheim \(Canada\) Ltd.](#) CCCEP Approved Chronic Obstructive Pulmonary Disease (COPD) continuing education (CE) program for pharmacists

Reference list. <http://www.lungcare.com/copd/references.htm>

Shiner RJ. Long-term oxygen therapy in COPD. COPD professional.org
http://www.copdprofessional.hmg.com/resource/clinical_topics/Long-term.htm

SUNY Upstate Medical University. New York Cochrane Reviews with special relevance to primary care

<http://www.upstate.edu/fmed/cochrane/cochabstracts.shtml>

Other teaching

The results have been used by the University of Toronto, Canada in an educational web site for GPs, patients and carers that I have adapted for Australia.

The results of the study used as a basis for teaching evidence-based medicine at the University of Oslo, Norway by the immediate past president of the European Respiratory Society.

Results were presented in a series of lectures at:

Institute of Tuberculosis and Chronic Respiratory Disease, Poland

The Pneumology Research Centre, St Petersburg, Russia

GIMBE. Evidence Based Medicine Italian Group. Clinical interactive workshop. Riccione. Italy. 5-6 April 2002 Clinical decisions with proven effectiveness. <http://www.gimbe.org/riccione/BPCO.pdf>

Other citations

Lewis CA, Eaton TE, Young P, Kolbe J. Short-burst oxygen immediately before and after exercise is ineffective in nonhypoxic COPD patients. *Eur Respir J*. 2003 Oct;22(4):584-8.

Book citation Wedzicha W COPD Critical debates. Blackwell publishing 2003.

American Thoracic Society (2005) Statement on Home Care for Patients with
Respiratory Disorders.

American Journal Of Respiratory And Critical Care Medicine, v. 171 (12), pp. 1443-
64, June 2005

NOTE: This publication is included in the print copy of the thesis
held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.1164/rccm.2504001>