Technology Assessment

Technology Assessment Program

Long-Term Oxygen Therapy for Severe COPD

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Tufts-New England Medical Center EPC

Joseph Lau, MD
Priscilla W. Chew, MPH
Chenchen Wang, MD, MS
Alexander C. White, MD

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BACKGROUND

Oxygen is an essential component of oxidative metabolism and is used as a treatment in patients with chronic lung disease. Chronic obstructive lung disease (COPD) is the most common chronic lung disease in the US and is the most common indication for supplemental oxygen. Criteria have been developed to help identify patients with COPD who may benefit from long-term oxygen therapy (LTOT). These criteria are based on the known detrimental pathophysiological effects of chronic hypoxemia. The hemoglobin molecule carries the majority of oxygen in the blood and is exquisitely designed to remain more than 90% saturated with oxygen provided the partial pressure of oxygen (PaO_2) in arterial blood is close to or above 55 to 60 mm Hg. Once the PaO_2 in arterial blood starts to fall below the 55 to 60 mm Hg threshold there is a steep reduction in the saturation of the hemoglobin molecule. Hemoglobin saturations of less than 90% are thought to result in a significant reduction in tissue oxygen delivery. By increasing the concentration of oxygen in inhaled air, supplemental oxygen improves both the PaO_2 of oxygen dissolved in arterial blood and the degree of oxygen saturation of the hemoglobin molecule (SaO_2). These effects in turn improve the oxygen delivery to organs and tissues allowing oxidative metabolism to continue in the setting

of chronic lung disease. The criteria based on these physiological observations have been developed in an attempt to identify patients who may benefit from supplemental oxygen by preventing deaths due to chronic hypoxemia and heart disease related to cor pulmonale. It is generally accepted that COPD patients with $PaO_2 \leq 55$ mmHg, or those with PaO_2 of 56 to 59 mmHg with evidence of end organ disease (e.g., pulmonary hypertension, cor pulmonale, polycythemia (hematocrit > 55%), arrhythmias, congestive heart failure, or impaired mental status) benefit from supplemental oxygen.

The cost to the health care system of providing supplemental oxygen to patients with COPD for up to 24 hours per day for many years is substantial. These costs include the cost of oxygen itself, the oxygen delivery systems to allow the patients to use the oxygen during activities of daily living or at night, and the many private vendors who service the equipment and monitor the patients.

CMS has developed a national coverage policy in 1985 based on discussions with experts and clinical evidence. CMS presently requested a technology assessment from AHRQ to summarize the available clinical and scientific evidence on the appropriateness and effective use of LTOT in patients with COPD. This summary will be presented as background for

discussion to an expert working group convened by NHLBI to discuss LTOT. In particular, CMS would like the report to address the following issues:

- Identify and analyze studies of long-term oxygen use that may have substantial impact on public health or health care costs.
- Identify and analyze studies that examine the efficacy or effectiveness of long-term oxygen on specific indications, in particular COPD.
- Identify and analyze studies to determine if long-term oxygen therapy is beneficial, and if there are any adverse effects to long-term oxygen therapy.
- Identify and analyze studies that examine the impact of long-term oxygen therapy on the progression of COPD.
- Address any addition specific assessment questions formulated by the project team in consultation with AHRQ.

METHODS

We conducted a systematic review of the literature to identify clinical studies in humans to address the above issues. The research questions could be succinctly rephrased as: What is the evidence on the outcomes and adverse effects in COPD patients treated with LTOT? In consultation with representatives from AHRQ, CMS, and NHLBI, we developed the following literature review criteria. These criteria include specifications of design, patient population/disease characteristics, types of LTOT and comparators, and outcomes of the studies to be reviewed.

Inclusion Criteria for Outcomes Studies

We accepted studies that reported the evaluation of LTOT in hypoxemic COPD patients on relevant outcomes of interest. Specific criteria for the patient population, interventions, outcomes, and study designs are discussed below.

Hypoxemic COPD Patients

We included LTOT studies of adult COPD patients based on 3 levels of hypoxemia: PaO_2 (mmHg) ≤ 55, 56 – 59, and 60 – 64. We accepted the definition of COPD as defined by the study authors, this generally included

patients with chronic bronchitis and emphysema. FEV_1 or % of predicted FEV_1 were not used as an entry criterion in our report. Studies that used the inclusion criteria of $PaO_2 \leq 55$ mmHg also typically included patients with PaO_2 between 56 and 59 if they demonstrated evidence of tissue hypoxia. We included cohort studies that evaluated mixed population (e.g., cancer, heart failure) if they reported stratified data for COPD patients or if at least 80% of the patients have COPD at hypoxemic levels of our interest.

Long-term Oxygen Therapy

LTOT is the use of oxygen outside the hospital setting in patients with COPD who are otherwise medically stable. Oxygen can be given while the patient is at rest, ambulating or sleeping at night. Oxygen may be delivered to the patient via nasal cannula, facemask, non-invasive positive pressure ventilation, or through the transtracheal route. It is generally accepted that patients who meet the criteria for LTOT should receive continuous supplemental oxygen 24 hours per day. However, the minimum number of hours of oxygen use needed to qualify for LTOT is not well defined. In addition, the number of hours of actual use of LTOT each day is dependent on patient adherence. For the purpose of this report we included all studies that were defined by the study authors as LTOT, including studies that

used nocturnal oxygen only. We included studies that provided oxygen using refillable cylinders, concentrators, or liquid oxygen systems.

Outcomes

Outcomes assessed in this report included survival and non-survival outcomes. Non-survival outcomes include: hospitalization episodes, length of stay, quality of life, exercise capacity, neuro-cognitive outcomes, depression, changes in pulmonary function (e.g., FEV_1) and other physiologic measurements (e.g., pulmonary artery pressure, hematocrit), and progression of pulmonary hypertension (cor pulmonale). In consultation with NHLBI staff, PaO_2 and $PaCO_2$ were not included as outcomes of interest.

Study Design

We included randomized controlled trials (RCTs) to provide direct comparisons of LTOT with standard care or alternative interventions. Prospective and retrospective cohorts (including LTOT patients registries) of patients using LTOT are used to derive additional information about survival and to compare baseline with follow-up results of various endpoints. For mortality outcomes, the percentages of mortality or survival

at defined time periods in the cohort were extracted. To qualify for evidence to be used for non-survival outcomes, cohort studies must report either results at baseline and at follow-up, or results of a defined comparison group. The LTOT arm of a RCT that do not meet the inclusion criteria (e.g., the main purpose of a study was to compare modes of oxygen delivery rather than the effects of LTOT) may nonetheless be included as a prospective cohort to provide additional information on survival and other outcomes. To be considered, each study must have at least 10 patients in each study arm (i.e., 10 in a cohort study and 20 in a parallel group randomized trial). To be considered for survival outcome, a study must have followed patients for at least 6 months.

Inclusion Criteria For Adverse Effect Studies

We accept adverse effects data in all the studies evaluated for clinical outcomes and any study that explicitly reported on adverse effects attributed to oxygen use. We excluded adverse effects related to oxygen delivery methods (e.g., complications of transtracheal method).

Excluded Studies

We excluded studies in which the main purpose was the evaluation of LTOT in patients with kyphoscoliosis or obesity-related obstructive sleep apnea, comparisons of different forms of oxygen delivery systems, or the evaluation of other interventions without outcomes specific to LTOT arms. Cross-sectional studies that do not provide longitudinal follow-up data for comparisons are excluded.

Several sets of articles were publications on the same or overlapping populations. From each set, we selected the article with the most comprehensive reporting of data and used other articles for supplemental information.

Literature search

We performed a MEDLINE search on February 27, 2004 for English language studies that evaluated the use of LTOT in patients with COPD. Search terms related to “long-term” included: ambulatory, continuous, domiciliary, home, long-term, and nocturnal. In addition, we reviewed the references of published systematic reviews, retrieved clinical trial articles, selected review articles, and clinical practice guidelines on this topic for potentially relevant studies.

Evidence Tables

Data extracted from each study that met the review criteria are summarized in evidence tables included in the appendix of this report. The evidence tables provide information for each of the studies on selected baseline patient characteristics, inclusion and exclusion criteria, study design, intervention, comparator, and outcomes. Evidence tables are grouped according to their study designs (randomized controlled trials or cohort studies) and then according to the 3 PaO_2 levels. Within each evidence table, the studies are ordered chronologically in ascending order according to their publication year.

RESULTS

The MEDLINE search yielded a total of 1,575 citations. After reviewing the abstracts, we retrieved 146 full articles for further evaluation. Thirty-nine studies that met the final inclusion criteria are summarized in this report. Six randomized controlled trials (RCTs) involving 541 patients and 24 prospective and 10 retrospective cohort studies with about 25,000 patients reported on deaths and other outcomes. Data from these studies are shown in Evidence Tables 1-4 in the appendix.

We describe in this section the results of the studies grouped by 3 levels of PaO_2 (mmHg): ≤ 55, 56 – 59, and 60 – 64. Within each of the PaO_2 levels, mortality results are presented first followed by other outcomes. Table 1 below summarizes the number of studies and outcomes available in each of the PaO_2 levels.

Table 1. Studies of LTOT for COPD Patients Included in this Report

	RCTs # studies (# patients)		Cohort Studies # studies (# patients)	
Population PaO_2 mmHg	Mortality	Other Outcomes	Mortality	Other Outcomes
≤ 55	**2 (n=290)** NOTT 1980 MRC 1981	**Hospital admission** **2 (n=290)** NOTT 1980 MRC 1981 **HRQL** **1 (n=203)** NOTT 1980, 1983 **Exercise capacity** **1 (n=10)** Cuvelier 2002 **Pulmonary function** **3 (n=320)** Fleetham 1980 NOTT 1980 MRC 1981	**17 prospective cohorts (n=6,723)** Krop 1973 Ashutosh 1983 Weitzenblum 1985 Vergeret 1989 Gorecka 1992 Dubois 1994 Dallari 1994 Simonds 1995 Oswald-Mammosser 1995 Borak 1996 Clini 1996 Okubadejo 1996 Heaney 1997 Aida 1998 Strom 1998 Zielinski 1998 Farrero 2001 **8 retrospective cohorts (n=18,300)** McKeon 1987 Corrado 1994 Buyse 1995 Miyamoto 1995 Chailleux 1996 Hjalmarsen 1999a Crockett 2001 Demirel 2003	**Hospital admission** **4 (n=319)** Stewart 1975 Weitzenblum 1985 Clini 1996 Ringbaek 2002 **HRQL** **6 (n=223)** Krop 1973 Lahdensuo 1989 Borak 1996 Okubadejo 1996 Hjalmarsen 1999b Farrero 2001 **Sleep** **1 (n=12)** Lin 1996 **Pulmonary function** **8 (n=200)** Krop 1973 Weitzenblum 1991 Simonds 1995 Clini 1996 Okubadejo 1996 Farrero 2001 Sergi 2002 Bratel 2003
56 – 59	ND	ND	**prospective cohorts** **1 (n=46)** Sliwinski 1992	**Pulmonary function** **1 (n=14)** Sandek 2001 **Hospital admission** **1 (n=46)** Sliwinski 1992

	RCTs # studies (# patients)		Cohort Studies # studies (# patients)	
Population PaO_2 mmHg	Mortality	Other Outcomes	Mortality	Other Outcomes
60 – 64	**2 (n=211)** Gorecka 1997 Chaouat 1999	**Pulmonary function** **1 (n=76)** Chaouat 1999	**retrospective cohorts** **1 (n=48)** Hjalmarsen 1999a	ND

ND – no data
HRQL – health related quality of life

Patients with PaO_2 ≤55 mmHg

Two RCTs enrolled 290 COPD patients with PaO_2 ≤ 55 treated with LTOT reported data on mortality outcomes (NOTT 1980, MRC 1981). Seventeen prospective cohort studies with a total of 6,723 COPD patients with PaO_2 ≤ 55 treated with LTOT reported mortality data (Table 2).

Mortality Outcomes - RCTs

The Nocturnal Oxygen Therapy Trial (NOTT) selected 203 patients from 1,043 patients with hypoxemic COPD evaluated in 6 centers (NOTT 1980). One hundred and two patients were randomized to receive nocturnal oxygen therapy (NOT) and 101 patients to continuous oxygen therapy (COT). Patients were randomized in blocks of 4 within each study center. Neither the investigators nor the patients were blinded. Oxygen was delivered via nasal prongs using oxygen concentrators, liquid oxygen systems, or compressed gas. Patients were evaluated at baseline and every 6 months thereafter.

Seventy-nine percent of the patients were male and the average age was 65 years. The baseline general and cardiopulmonary characteristics were well balanced between the study groups with mean PaO_2 of 51.5 mmHg in the NOT group and 50.8 mmHg in the COT group, mean $PaCO_2$

of 43 mmHg and % predicted FEV_1 of 30 in both groups. The overall baseline rating of the neuropsychiatric characteristics was higher in the NOT group compared with the COT group (4.5 vs. 4.2) and was marginally significant (P=0.06).

Surviving patients were followed for a minimum of 12 months with a mean of 19 months. Adherence to oxygen therapy was noted to be “very good”. Patients in the COT group received an average of 18 hours and patients in the NOT group received 12 hours of oxygen therapy daily. Overall, 21 patients died in the COT group and 41 patients died in the NOT group. The 12-month mortality was 12% in the COT group and 21% in the NOT group (odds ratio 0.53, 95% CI 0.25-1.11). At 24 months, the mortality was 22% in the COT group and 41% in the NOT group (odds ratio 0.45, 95% CI 0.25-0.81).

The Medical Research Council trial from UK randomized 87 patients in 3 centers to receive LTOT or no placebo/supplemental-oxygen controls (MRC 1981). Oxygen was administered via nasal prongs using oxygen concentrators, liquid oxygen systems or oxygen cylinders for at least 15 hours/day in the treatment group. Neither the investigators nor the patients were blinded.

Forty-two patients were randomized to LTOT and 45 patients served as no-treatment controls. The average age was 58 and 76% of the patients were men. The mean baseline PaO_2 measurements of the 2 groups were similar (50.2 mmHg in the LTOT group vs. 51.6 mmHg in the control group). The mean baseline FEV_1 in men who received LTOT was slightly higher than the control (0.76 L vs. 0.65 L). Although the mean baseline $PaCO_2$ was similar between groups (55 mmHg), this was higher than that of the NOTT study population (43 mmHg).

During a 5-year follow up, 19 of the 42 patients (45%) on LTOT died, compared with 30 of the 45 controls (67%) (odds ratio 0.42, 95% CI 0.18-0.98). The benefit for men was not seen until after 500 days whereas the benefit for women was demonstrated almost immediately. One patient was withdrawn from the LTOT group due to failure to comply.

The patients in both trials were mostly similar and they achieved similar degree of mortality reduction. However, the control group in the NOTT trial used NOT whereas the control group in MRC trial had no supplemental oxygen. While one can conclude that at least 15 hours of COT is beneficial, one cannot directly infer that there is a continuous dose effect (i.e., whether 18 hours of COT is better than 15 hours or whether 12 hours of NOT is better than no supplemental oxygen).

Table 2. Cohort studies that reported mortality data of LTOT for COPD patients with $PaO_2 \leq 55$ mmHg

Study Year Country	Study Size	Study duration (years)	Mortality %			
			1 y	2 y	3 y	5 y
Prospective Cohort Studies						
Aida 1998 Japan	4,552	6	12	38		61
Strom 1991, 1993, 1998 Sweden	405	2.3	23	44		62
Gorecka 1992 Poland	315	1	21			
Dubois 1990 1994 Belgium	270	3	30	50	57	83
Heaney 1997 N Ireland	178	> 8	31 (10 mo)	50 (20 mo)		67
Dallari 1994 Italy	166	2		22	33	
Borak 1996 Poland	1224	1	27			
Zielinski J 1998 Poland	95	6		23		
Oswaldmammosser 1995 France	84	5			29	52
Vergeret 1989 Denmark	75	2	12			
Farrero 2001 Spain	62	1	34			
Simonds 1995 England	33	5	15	24	32	55
Okubadejo 1996 UK	23	0.5	17 (6 mo)			

Study Year Country	Study Size	Study duration (years)	Mortality %			
			1 y	2 y	3 y	5 y
Clini 1996 Italy	34	1.5	17-23			
Ashutosh 1983 USA	28	2		Responders 13 (n=17) Non-responders 78 (n=11)		
Weitzenblum 1985 1991 France	24	1			25 (33 mo, n=16)	65 (73 mo)
Krop 1973 Stewart 1975 US	12	2	8.3	33		
Retrospective Cohort						
Chailleux 1996 2003 France	12,403	10	~25	~41	~70	
Miyamoto 1995	5,055	7	~13	~25	~36	~58
Crockett 2001 Australia	505	10	25	49		81
Demirel 2003 Turkey	127	1.4	5.5			
McKeon 1987 Australia	84	14	6	20		64
Corrado 1994 Italy	35	4	~6	~17	~37	~49 (4 y)
Hjalmarsen 1999a Sweden	76	8		27		50
Buyse 1995 Belgium	15	3	13	40		

Mortality Outcomes - Cohort Studies

Seventeen prospective cohort studies were conducted in Australia, Europe, Japan, and the US (Table 2). These studies included a total of 6,723 patients with study size ranging from 12 to 4,552. The studies followed patients from 6 months to 12 years. LTOT therapy was generally given 14 to 24 hours daily. One study reported greater than 8 hours of oxygen at night and 1 study did not report oxygen usage data. The reported mortality varies between 6 to 34% at 1 year of follow-up in 12 studies, 20 to 50% at 2 years in 9 studies, 25 to 57% at 3 years in 5 studies, and 52 to 83% at 5 years in 7 studies. The largest prospective cohort study of 4,552 patients came from Japan with a mean follow up of 2.4 years (Aida 1998). They reported 1-, 2-, and 5-year mortality of 12, 38, and 61%, respectively.

Eight retrospective cohort studies with 6 months to 10 years of follow-up reported mortality outcomes in 18,300 patients (Table 2). Four studies reported patients were prescribed at least 15 hours of oxygen daily while the other 4 studies did not report this information. The range of mortality rates of the retrospective cohort studies at different follow-up time points are similar to those of the prospective cohort studies. The largest retrospective cohort study with 12,403 patients from France reported 1-, 2-, and 3-year mortality rates of 25, 41, and 70%, respectively (Chailleux

1996). The second largest retrospective cohort study of 5,055 patients was conducted in Japan (Miyamoto 1995). This study reported 1-, 2-, 3- and 5-year mortality rates of 13, 25, 36, and 58%, respectively. This study shared the same patient registry as the report by Aida et al. (1998) and probably had a large degree of overlap in the patients studied.

Other (non-mortality) Outcomes

Hospital Admission - RCTs

Two RCTs reported results on hospitalization. The NOTT and MRC trials both reported that LTOT decreases the number of days of hospitalization among hypoxemic COPD patients although neither trial reported results numerically. The NOTT study reported that patients on COT tended to be hospitalized less often and to have fewer long hospitalizations than NOT patients, although differences were not statistically significant (NOTT 1980). The MRC trial reported that the duration of hospitalization due to exacerbations of respiratory failure was not affected by oxygen therapy (MRC 1983).

Hospital Admission – Cohort Studies

Three prospective (Krop 1973, Weitzenblum 1985, Clini 1996) and 1 retrospective (Ringbaek 2002) cohort studies reported hospitalization data. All of these studies reported that LTOT reduced the frequency of hospitalization and the number of hospital days. Krop et al. (1973) reported that the average number of days hospitalized per patient decreased from about 30 days before LTOT to 20 days 1 year after LTOT oxygen was instituted in a cohort of 12 patients. In a cohort of 16 patients, Weitzenblum et al. (1985) reported that the average number of hospitalization days per year decreased from 18 to 9 after LTOT. Clini et al. (1996) compared two 18-month periods before and after LTOT in a cohort of 17 patients. They reported that the average number of hospital admissions decreased from 2 to 1 and the average number of days in hospital decreased from 55 to 18 after LTOT. In a retrospective cohort study of 246 patients that focused on the effect of LTOT on hospitalization, Ringbaek et al. (2002) reported that the average number of hospital admissions per patient per year decreased from 2.1 to 1.6 and he average number of days hospitalized decreased from 23.7 to 13.4 after LTOT. Similar magnitude of decreases were seen in patients who received 15-24 hours of oxygen daily compared with those who received less than 15 hours.

Health Related Quality of Life (HRQL) and Neuropsychological - RCT

The NOTT study was the only RCT that reported HRQL data. It assessed Minnesota Multiphasic Personality Inventory (MMPI) scale, Sickness Impact Profile (SIP) and Profile of Mood States (NOTT 1980). The study reported neuropsychological deficits in hypoxemic COPD patients and observed small ("average about 10%") improvements in neuropsychological function and quality of life scores when data from patients receiving COT or NOT were combined. The authors hypothesized that these small changes might have been due to the more intensive medical and nursing care that the patients received as study participants rather than the direct effect of oxygen. Numerical data for HRQL measures were reported for the baseline but not for the end of the trial.

Health Related Quality of Life (HRQL) and Neuropsychological – Cohort Studies

Six prospective cohort studies reported HRQL or neuropsychological outcomes on 223 patients (Krop 1973, Lahdensuo 1989, Borak 1996, Okubadejo 1996, Hjalmarsen 1999b, Farrero 2001). LTOT was provided for various durations from 3 months to 2 years in these studies. These studies reported HRQL and psychological and psychosocial response data,

including: MMPI, Wechsler Adult Intelligence Scale, Wechsler Memory Scale, Bourdon-Wiersma Test, Beck Depression Inventory, Chronic Respiratory Questionnaire, St. George's Respiratory Questionnaire, SIP and the Hospital Anxiety and Depression Scale (HADS).

The study by Borak et al. (1996) from Poland reporting data on 90 patients represents the largest cohort of COPD patients with PaO2 ≤ 55 mmHg that have been evaluated for neuropsychological status before and after the initiation of LTOT. Of the 124 initially eligible patients, cognitive function, psychological status, and attitudes were assessed before and after one year in 90 survivors using a battery of instruments. The authors found major cognitive dysfunction and severe emotional disturbances at baseline. Patients were found to have a low level of concentration, narrow interests, reduced planning ability, disturbed direct memory, and reduced visual/spatial coordination. After one year of oxygen therapy, improvements in cognitive function were limited to recent memory and speed of work. A significant improvement in self-esteem and emotional status were observed following treatment. It was noted that improvements in psychological status was observed despite some deterioration in pulmonary function. The authors also concluded that it is difficult to separate the effect of oxygen from the overall benefits of specialist medical care.

Two other small studies of 12 patients (Krop 1973) and 10 patients (Hjalmarsen 1999b) also reported that LTOT is associated with an improvement in intellectual functioning, depression and HRQL. The changes observed in these studies did not reach statistical significance due to the small study size. However, 3 other studies with a total of 111 patients) reported that there was no significant change in the HRQL and psychological and psychosocial variables in patients treated with LTOT (Lahdensuo 1989, Okubadejo 1996, Farrero 2001.

Sleep Outcomes

We identified only 1 prospective cohort study that investigated the effect of LTOT on sleep (Lin 1996). The study was conducted in Taiwan on 12 patients with severe COPD. Total sleep time, sleep efficiency, and sleep latency were compared before therapy and after 2 weeks of oxygen therapy. The study found that sleep efficiency and sleep architecture did not change with oxygen therapy.

Exercise Capacity

One randomized crossover study of 10 COPD patients on LTOT reported physical exercise capacity outcome (Cuvelier 2002). The patients

performed 3 successive 6-min walking tests separated by 60 minutes of rest. The first test was conducted in room air and the other tests in a random order with 2 types of refillable oxygen cylinders. Mean walking distance was significantly increased when performed with either cylinders (375±97 meters [p=0.02] or 374±81 meters [p=0.03]) compared with room air (335±90 meters).

Pulmonary Function and Physiologic Measurements – RCTs

Three RCTs (Fleetham 1980, NOTT 1980, MRC 1981) reported on pulmonary function and physiologic measurements. Fleetham randomized 30 COPD patients to treatment with either 12 hours of NOT or 24 hours of COT (Fleetham 1980). There were no significant changes in pulmonary function (FEV_1%) in either group over the 6 months period. Among patients who received LTOT in the MRC trial, the red cell mass fell slightly and the mean PAP remains unchanged, whereas in the control group the red cell mass and the PAP rose. These changes were not significantly different between groups. The NOTT study reported that in patients who received COT, comparing with patients who received NOT, the pulmonary vascular resistance was significantly decreased at 6 months (-11% vs. +6.5%;

p=0.04). Hematocrit was also significantly decreased in the COT group when compared with the NOT group (9.2 % vs. 2%, p=0.008).

Pulmonary Function and Physiologic Measurements – Cohort Studies

Eight prospective cohort studies (Krop 1973, Weitzenblum 1985, Simonds 1995, Clini 1996, Okubadejo 1996, Farrero 2001, Sergi 2002, Bratel 2003) reported pulmonary function data on 218 patients. No significant changes were reported in FEV_1% in 5 studies (Krop 1973, Weitzenblum 1985, Simonds 1995, Clini 1996, Okubadejo 1996) while 2 other studies (Farrero 2001, Sergi 2002) found significant improvements in FEV_1%. Bratel reported a non-significant decrease in hemoglobin (15.1 g to 14.6 g) and no change in FEV_1% in 12 patients.

Patients with PaO_2 between 56 and 59 mmHg

Mortality Outcomes

There was no RCT in this category of PaO_2. One prospective cohort study of 46 COPD patients with mean PaO_2 of 57 mmHg investigated whether the acute effect of oxygen on pulmonary arterial pressure (PAP) is related to survival (Sliwinski 1992). Patients who experienced a decrease of 5 mmHg or more of PAP while breathing supplemental oxygen were classified as responders. After 2 years of LTOT, 12 patients died in the non-responders group (39 patients) and 3 died in the responders group (7 patients). The 2-year survival rate was 69% in non-responders and 57% in responders.

Hospital Admission

The study by Sliwinski (1992) also assessed the relationship of responders to LTOT (based on PAP changes) with hospitalization. After 2 years of LTOT, the subjects from the non-responders group were admitted to the hospital 55 times versus 6 times in the responders group during the study period of 2 years. On average there were 1.4 versus 0.8 admissions per patient in the non-responders versus responders group.

Pulmonary Function and Physiologic Measurements

We found 1 prospective cohort studies in this category of $PaCO_2$ reporting the effect of LTOT on pulmonary function and physiological measurements. In a study of 14 COPD patients receiving 6 months of LTOT (Sandek 2001), no significant changes in dynamic or static lung volumes, hypercapnic ventilatory response or hypercapnic drive response were detected. The author concluded that 6 months of low flow oxygen therapy in stable COPD patients is not accompanied by any clinically important changes in pulmonary physiology.

Patients with PaO_2 between 60 and 64 mmHg

Mortality Outcomes - RCT

Two RCTs reported mortality outcomes in this category of PaO_2. One RCT evaluated 76 COPD patients in 6 hospitals in 4 European countries (Chaouat 1999). Forty-one patients were randomized to oxygen concentrator for 8-10 hours per night and 35 patients to no oxygen control group. There was no significant difference in mortality between the treated and control groups on an intention to treat analysis (odds ratio 1.1, 95% CI 0.37-3.4). The second trial randomized 135 patients into LTOT (at least 17 hours of oxygen daily) or usual care (Gorecka 1997). The patients were followed for 3 years or until death. No significant difference in mortality was found between the 2 groups (odds ratio 1.1, 95% CI 0.37-3.4).

Mortality Outcomes - Retrospective cohort

Hjalmarsen et al. (1999a) analyzed a retrospective cohort of 124 patients using LTOT for 6 years by dividing it into 2 groups with $PaO_2 \leq 55$ mmHg and $PaO_2 \geq 56$ mmHg (mean $PaO_2 = 62$ mmHg). Both groups had similar FEV_1 and FVC levels. The 2- and 3-year survival rates were 73% and 50%, respectively, in the $PaO_2 \leq 55$ group, and 78% and 40% in the $PaO_2 \geq 56$ group. The author concluded that survival during LTOT was

similar in patients with and without severe hypoxemia at the same level of loss of lung function.

Pulmonary Function and Physiologic Measurements

The RCT by Chaouat (1999) also collected pulmonary function and physiologic measurements. It reported no significant changes in FEV_1, resting and exercising PAP between LTOT and control groups.

Adverse Effects of LTOT

Two studies reported adverse effects and safety concerns with the use of LTOT. One study reported: “A negative psychological impact on the patients caused by the oxygen treatment was reported in a small proportion of the follow-up recordings (0-9%)” (Strom 1991). However, this issue was not expanded upon in the article.

One retrospective review of burn patients reported a subgroup of 23 LTOT patients with burn injuries directly related to use or handling of oxygen (Chang 2001). In this study, COPD was the most prevalent reason for home oxygen use (20 of the 23 patients). The mean age was 70 years with a range of 50 to 84 years. Causes of fire included cigarette smoking (16/23), cooking (6/23), and refilling a home oxygen unit with liquid oxygen (1/23). Twenty-one of 23 sustained partial-thickness injuries involving an average of 4% of the body surface area. Inhalation injury occurred in 13 patients with 5 of them requiring tracheal incubation and mechanical ventilation because of a combination of direct inhalation injury, acute worsening of their underlying pulmonary disease, and subsequent lung infection. Two of the 23 patients died during their hospitalizations. Both were injured while smoking during the use of their home oxygen.

CONCLUSIONS

Evidence from RCTs to guide the use of LTOT in patients with COPD is very limited. Most of the studies included in this report focused on the severely hypoxemic populations with $PaO_2 \leq 55$ mmHg. Only 2 RCTs published over 20 years ago evaluated patients with PaO_2 between 56 and 59 mmHg. Both of these trials reported similar reduction of overall mortality. Two RCTs conducted in patients with PaO_2 between 60 and 64 mmHg reported no mortality benefits.

Twenty-five prospective or retrospective cohort studies with almost 25,000 patients reported survival data for COPD patients with $PaO_2 \leq 55$. It can be readily appreciated from these cohort studies that the overall survival in the severely hypoxemic population on LTOT is poor, compared with the normal population. The survival rates at any common time point varied widely across the studies suggesting that large variations exist in the inclusion criteria, populations studied, forms of intervention, and assessment of outcomes. This degree of heterogeneity and the lack of a comparison group make it difficult to generalize the results of individual studies.

Limited evidence from RCTs and cohort studies on non-mortality outcomes in patients with $PaO_2 \leq 55$ mmHg suggest that LTOT may reduce

the number of hospital admission or the length of hospitalization, improve certain aspects of neuropsychological function.

Serious adverse effect appears to be limited to the well-known problem that oxygen is highly flammable and should not be used around open flames. Occasional thermal burn injuries may also occur with handling of liquid oxygen systems.

It is unnecessary to conduct additional placebo controlled RCTs in patients with PaO_2 ≤55 mmHg. However, there is currently no randomized evidence of survival benefit in patients with PaO_2 56-59 mmHg. The methodological quality of the studies could be substantially improved. Better standardization of inclusion criteria and outcome measures will facilitate the interpretation of results across studies. Several studies have analyzed clinical and physiologic measures as predictors of responses to survival and non-survival benefits in LTOT users. A priori stratification by potential predictors of outcomes might be useful to gain insights to optimize management.

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Long-term Oxygen Therapy for COPD

Evidence Tables

Evidence Table 1. Randomized controlled trials of LTOT for COPD patients with PaO_2 ≤55 mmHg

Study Year Country	Study design		Population	Baseline		O_2 therapy hrs/day	Outcomes		Comments
	Duration; RCT features	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Fleetham 1980 Canada	1 y F/U	Inclusion: FEV_1/VC < 70%, and if TLC ≥80% P nl, PaO_2<56 or <59 mmHg w/ankle edema > 3 wk of infection-free clinical stability on intensive bronchodilator	N=16 Male: ND Age: ND	PaO_2 52±0.7 $PaCO_2$ 46±1.2	25±2.9 SE	COT 24	ND	*Pulmonary function at 6m* FEV_1% 25±2.9 (SE) NS n=11	Oxygen compliance monitored by nurses, no patients lost to F/U
			N=14 Male: ND Age: ND	PaO_2 52±1.3 $PaCO_2$ 44±1.5 SE	22±2.3 SE	NOT 12		FEV_1% 21±3.3 (SE) NS n=12	
NOTT 1980 Heaton 1983 US	19.3 mo average F/U; Block randomization within each 6 sites	Inclusion: >35 y, clinical diagnosis of COPD, PaO_2 ≤ 55 mmHg or $PaCO_2$ ≤ 59 plus edema, hematocrit ≥ 55%, P pulmonale on ECG, FEV_1/FVC <70%, TLC ≥ 80% predicted Exclusion: previous O_2 12h/d for 30 d prior 2 m, other disease that might influence outcomes	Total N=203 COT n=101 NOT n=102 Male: 79% Age: 65	COT PaO_2 51 $PaCO_2$ 43	COT 30	COT 18±4.8	*12 mo* COT 12%±3.2 (SE) NOT 21%±4.0 (SE) odds ratio 0.53 (0.25-1.11) *24 mo* COT 22%± 4.6 (SE) NOT 41%±5.5 (SE) odds ratio 0.45 (0.25-0.81)	*Hematocrit decrease at 18 mo* NOT (n=36) 2.0% COT (n=40) 9.2% p=0.008 *Pulmonary vascular resistance at 6 mo* NOT (n=49) +6.5% COT (n=52) -11% p=0.04 *Neuropsychological evaluation at 6 mo (n=150)* Small improvements noted in most measures but formal statistical test were not presented for two treatment groups. *HQOL* NS for either groups on QOL measures *Hospitalization* COT decrease trend for number of admissions and LOS compared to NOT but NS.	2 COT patients lost to F/U
				NOT PaO_2 52 $PaCO_2$ 44	NOT 30	NOT 12±2.5			

Study Year Country	Study design		Population	Baseline		O_2 therapy hrs/day	Outcomes		Comments
	Duration; RCT features	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
MRC Stuart-Harris 1981 UK	5 y F/U; table of random numbers, unblinded	Inclusion: <70, chronic bronchitis or emphysema with FEV_1 <1.2L, PaO_2 40- 60 mmHg Exclusion: fibrotic or infiltrative lung disorder, pneumonconiosis, severe kyphoscoliosis, pulmonary embolism, elevated BP, coronary arterial or other life-threatening disease	N=87 Treatment: 42 Control: 45 Male: 76% Age: 58 (42-69)	PaO_2 51 $PaCO_2$ 54	FEV_1 L ~0.6 W ~0.7 M	>15	5 years Treatment: 45% Control: 67% OR 0.42 (0.18, 0.98)	"There are no significant different between the groups in physiological variables, hospital stay and work record."	3 centers 1 withdrawal from treatment group
Cuvelier 2002 France	ND; Cross-over, double dummy, single-blind	Inclusion: stable COPD, LTOT at home, able to perform walking tests	N=10 Male: 90% Age: 65	PaO_2 55± 6.3 $PaCO_2$ 46± 7.4	98± 27	ND	ND	Mean walking distance test Room air 334.5±90m (A) O_2 374±81 m p=0.03 (B) O_2 375±97 m p=0.02	---

Mean and standard deviation unless otherwise noted.
Abbreviations: COT, continuous oxygen therapy; d, day(s); F/U, follow-up; LOS, length of stay; m, month(s); ND, no data; NOT, nocturnal oxygen therapy; OR, odds ratio; PAP, pulmonary artery pressure; SE, standard error; y, year.

Evidence Table 2. Randomized controlled trials of LTOT for COPD patients with PaO_2 60-64 mmHg

Study Year Country	Study design		Population	Baseline		O_2 therapy hours/day	Outcomes		Comments
	Duration / RCT features	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 % Predicted		Mortality	Other outcomes	
Gorecka 1997 Poland	7 y F/U, mean 41 mo; Computer central generated random numbers, not blinded	Inclusion: single diagnosis COPD, 40-80 y with airway limitation (FEV_1/VC post bronchodilator of <70%, PaO_2 56-65 from 1987-92, F/U through 1994 Exclusion: serious disease of organs other than lungs that might influence survival	N=135 Male: 76% Age: 61	PaO_2 60±2.8 $PaCO_2$ 44±6.7	30±9.8	14	LTOT 56% Control 49% Odds Ratio (all-cause) 1.4 (0.70–2.7)		9 regional LTOT centers, no patients lost to F/U
Chaouat 1999 Europe	35 mo F/U Table of random sampling numbers, NOT to even numbers, control to odd numbers, unblinded	Inclusion: FEV_1/VC ratio <60% predicted value, 2 PaO_2 measures 56-69 (4 weeks apart), $PaCO_2$ ≥45, nocturnal desaturation ≥ 30% & SaO_2 < 90% Exclusion: left or congenital heart, or interstitial lung diseases, bronchiectasis, disease that might affect outcomes, sleep apnea	N=76 Male: ND Age: 63 NOT: 41 No NOT control: 35	PaO_2 63±3.3 $PaCO_2$ 45±5.6	39±16	NOT 8.9±1.9	NOT 22% Control 20% Odds Ratio 1.1 (0.37-3.4)	There was no significant change in pulmonary volumes, FEV_1 and resting and exercising PAP	12 NOT & 10 controls received LTOT due to fall in PaO_2 levels, mortality analyses on intention to treat, similar results if LTOT exposure removed, 6 outpatient centers, 11 withdrawals, 2 lost to F/U

Evidence Table 3. Cohort studies of LTOT for COPD patients with PaO_2 ≤55 mmHg

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Prospective									
Krop 1973 Stewart 1975 US	25.2 mo F/U (4 - 40)	Inclusion: COPD, PaO_2 < 55 mmHg under optimal therapy, additional PaO_2 decrease with treadmill exercise, relief of hypoxemia with 2 L/min O_2 therapy	N=12 Male: 100% Age: 55 (33-64)	PaO_2 49±5.0 $PaCO_2$ 44±6.9	FEV_1 L 0.68±0.15	24	1y 8.3% 2y 33% (graph estimates)	*Survival* 56% at 2½ y *Pulmonary function (n=11)* NS for $PaCO_2$, FVC, FEV_1 *Hospital days* ~30 days/patient before LTOT (n=11) ~20 days/patient 1 year after LTOT (n=10) *Quality of life at 1 month* Pre / Post WAIS or W-B FSIQ 97.0 103.1 p<.05 VIQ 99.0 103.3 NS PIQ 93.6 102.0 p<.01 WMS 97.8 105.6 p<.01 B-G 23.0 9.2 p<.01 Bfp 24.8 9.9 p<.005 FRT 7.4 7.5 NS FT(T) 29.4 41.8 p<.005 MMPI Depression 24.9 18.4 p<.05 Hypochondriasis 20.7 14.2 p<.005 Hysteria 24.8 17.4 p<.025 Social introversion 27.5 20.0 p<.05 Diaries - all report ADL improvement	VA patients, no patient lost to F/U

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Ashutosh 1983 USA	2 y F/U	Inclusion: FEV_1 < 2 SD predicted value and FEV_1/FVC% < 70%, right heart failure, mean PAP > 20 mmHg, pulmonary capillary wedge pressure < 15 mmHg Exclusion: left ventricular disease	Responders PAP: 37±12 N=17 Male: ND Age: 57	PaO_2 53±8 $PaCO_2$ 46±9	FEV_1 L 0.94±0.51	Prescribed > 18	2 y 13%	*Survival* Significant for responders (reduction in pulmonary hypertension) over non-responders, p<0.005	Significant change of PAP > or < 5 mmHg while breathing 28% O_2 for 24 h used to divide patients into 2 groups; 1 withdrawal
			Non-responders PAP: 33±12 N=11 Male: ND Age: 60	PaO_2 54±12 $PaCO_2$ 46±10	FEV_1 L 0.83±0.58	Prescribed > 18	2 y 78%		2 withdrawals

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Weitzenblum 1985 1991 France	11.5 y F/U, 44±30 mo of therapy (12-120)	Inclusion: history of chronic bronchitis, air-flow obstruction < 1.5 L, hypoxemia & PaO_2 < 60 mmHg & clinically stable at 3 monthly measures, right heart failure or right ventricular hypertrophy, Ppa>20 mmHg, ≥ 1 y between catheterization before & after onset of LTOT, compliance (>15 h/d) Exclusion: left heart disease, systemic hypertension, chronic pulmonary or severe disease	N=24 Male: 92% Age: 59 (41-74)	PaO_2 52±6.5 $PaCO_2$ 49±8.2	34±14	18	33 mo 25%* 73 mo 54% *Denominator= 16	*Hospital days per year (n=16)* Pre-LTOT 18±16 Post-LTOT 9±19 0.10 > p > 0.05 (NS) *Pulmonary function* FEV_1 % 33±13 NS (compared with baseline) *Pulmonary arterial hypertension* Pre-LTOT 27 ±9.1 Post-LTOT 24±7.1 ns (compared to baseline)	Ambidirectional study, recruitment & consent given between 2nd and 3rd catheterization, no data on number of pts from onset of LTOT for mortality or dropouts before study enrollment

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Vergeret 1989 Denmark	1 y F/U	Inclusion: 40-75 y, severe COPD $FEV_1/FVC<60\%$, total lung capacity >80% of reference values, $FEV_1<1L$ & stable chronic respiratory insufficiency PaO_2 <8kPa & >5.3kPa $PaCO_2$ <8.2kPa Exclusion: pts on portable O_2, > 3 admissions	Fixed O_2 N=75 Male: 84% Age: 63	PaO_2 54±7.5 $PaCO_2$ ND	FEV_1 L 0.8±7.4	14	1 y 12%	No significant clinical and functional differences between 2 groups.	8 withdrawals
			Portable O_2 N=84 Male: 90% Age: 61			17	1 y 18%		5 withdrawals
Lahdensuo 1989 Finland	6 mo F/U	Inclusion: severe COPD, stable disease, $PaO_2<55$ or 55-59 & hematocrit > 55, cor pulmonale, or history of ≥1 acute cardiac failure from cor pulmonale Exclusion: smoking in the past 3 mo	N=26 Male: 73% Age: 63	PaO_2 49±6.7 $PaCO_2$ 46±14	ND	Prescribed 24	ND	*Psychosocial response* BDI 18.2 vs 15.1 p<0.06 No significant changes were observed in any psychosocial measures including depression, general activity & independence, coping skills	---

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Dubois 1990 1994 Belgium	6 y	Inclusion: PaO_2 <55 in controlled steady state ≥3 wks, $PaCO_2$ did not increase "excessively" Exclusion: A severe disease that might be expected to influences short-term mortality. No patients has had previous LTOT	N=270 Male: 86% Age: 66	PaO_2 48±6 $PaCO_2$ 47±9	30±12	18	1 y 30% 2 y 50% 3 y 57% 5 y 83%* 6 y 83%* *(graph estimates)		---
Strom 1991 1993 1998 Sweden	28 mo F/U (15-45)	Inclusion: Stable adults treated for chronic hypoxemia w/LTOT, approx 7.5 kPa, resting > 8 kPa, registered 1/1/87 – 6/30/89	N=405 Male: 50% Age: 67	PaO_2 50 $PaCO_2$ 49	27±15	18	1 y 23% 2 y 44% 3 y 62% Severity subgroup (WHO score) 1 y 2 y S0 2% 32% S1 15% 30% S2 24% 51% S3-4 52% 81% (graph estimates)	*Hospitalizations* (no pre-post data) 44 days/year *Annual admissions* M 2.8±3.2 F 3.1±3.0 *Psychological impact* Negative impact on patient or patient/family caused by oxygen therapy, more common with gas cylinder or therapy > 16 h/d	Registry with no exclusion criteria for adults on LTOT, 60 withdrawals

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Gorecka 1992 Poland	1 y F/U	Inclusion: PaO_2 ≤55 or 56-65 if one of following is present: Hct ≥55%, radiological signs of pulmonary arterial hypertension, ECG signs of right ventricular hypertrophy	N=315 Male: 74% Age: 62	PaO_2 51± 8 $PaCO_2$ 51±11	FEV_1 L 0.79 ±0.31	>17	1 y 21%		12 regional centers, no patients lost to F/U
Dallari 1994 Italy	24 mo F/U (2-50)	Inclusion: COPD on LTOT from 1987-1992	N=166 Male: ND Age: 69	PaO_2 54±5.8 $PaCO_2$ 51±7.6	36±11.3	16-20	2 y 22% 3 y 33%	*Predictors* Multivariate stepwise regression analysis showed that RVSP, age, and FEV_1 were statistically significant independent predictors of survival.	---
Simonds 1995 England	1.6 y median for NIPPV (0.1-6.3) 5 y F/U	Inclusion: symptomatic, chronic hypercapnic respiratory failure unresponsive to O_2 therapy, progressive deterioration in symptoms & arterial blood gas tensions	N=180 33 COPD Male: ND Age*: 57 *Subgroup data	PaO_2 46±6.0 $PaCO_2$ 62±14	FEV_1 L 0.58±0.3	7.88 Random subset of 16 which included other respiratory disorders, 48% COPD used supple-mental O_2 therapy	1 y 15% 2 y 24% 3 y 32% 4 y 55% 5 y 55% (graph estimates)	*Pulmonary function* (n=30 COPD) NS for FEV_1 *Sleep quality** Very good 21% Average 67% Poor 5% *Adverse events** Inconvenience (20) Nasal/mask problems (10) Gastric distension (3) Noise (3) *no baseline data, includes all diagnoses	Pts may have transitioned from other O_2 therapy; NIPPV therapy started in hospital, 5 withdrawals

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Oswald-mannosser 1995 France	5 y (1-12 F/U)	Inclusion: COPD, FEV_1/VC ratio < 60%, TLC > 80% of predicted value Exclusion: Lung disease, (sequelae of pulmonary tuberculosis, pneumoconiosis), left health disease, obesity (BMI > 32), sleep apnea, or other severe disease	N=84 Male: 89% Age: 63	PaO_2 52±5.4 $PaCO_2$ 45±7.6	FEV_1 L 0.8 (0.3)	>16	3 y 29% 5 y 52%	*Survival rate* PAP <25 mmHg vs. PAP>=25 mmHg p<0.001 The level of PAP (together with age) is a good indicator of survival in COPD patients receiving LTOT	---
Borak 1996 Poland	1 y F/U	Inclusion: PaO_2 < 55 mmHg, or 55-65 if polycythemic	N=124 Male 68% Age: 56 (28-76)	PaO_2 55±6.2 $PaCO_2$ 47±8.2	FEV_1 L 0.88±0.44	15	27%	*Psychological impact (n=90)* Significant improvement, p<0.001, for: Bourdon-Wiersma Test – correct deletion Rey test remembered words Depression Anxiety Psychological tension General mood Self-esteem Attitude towards therapy, future & life goals Tests include VRT, MAS, Beck's Depression Scale, SOPER)	All baseline data for survivors only n=90, no patients lost to F/U

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Lin 1996 Taiwan	2 weeks of therapy	Inclusion: stable hypercapnia, $PaO_2 \geq 44$ mmHg, $FEV_1P<70\%$, FEV_1/FVC <70%, FEV_1/FVC < 50% predicted, $PaO_2 < 55$ mmHg, or PaO_2 >55-60 right heart failure & polycythemia Exclusion: sleep apnea with hypopnea index ≥10, >15% increase in FEV_1, CNS, neuromuscular, CHF, endocrine, renal, or unstable disorders < 1 mo	N=12 Male: 58% Age: 65	PaO_2 52±2.5 $PaCO_2$ 51±3.5	ND	24		*Sleep stages/efficiency** NS for the following (compared to baseline): Sleep efficiency Sleep latency Arousal index Movement index Snore index Total sleep time Stage 1 through 4 REM *All therapy in hospital	No patients lost to F/U
Clini 1996 Italy	18 mo of therapy	Inclusion: COPD on LTOT ≥ 18 months, chronic hypercapnia, $PaCO_2 > 50$, ≥ one hospital admission due to severe exacerbation in past 18 months Exclusion: ≥ 15% increase FEV_1	LTOT N=17 Male: 53% Age: 67	PaO_2 50± 4.5 $PaCO_2$ 48 ± 6.8	33±10	>8 nightly	18 mo 18%	*Pulmonary function at 18 months* FEV_1 % (compared with baseline) LTOT 32±13 NS Historical LTOT 28±13 NS *Hospital admission* Comparison to 18 months prior to the study LTOT 2.0±0.7 vs 1.0±0.9 p<0.005 Historical LTOT 1.5±0.7 vs 1.5±1.1 NS *Days in hospital* Comparison to 18 months prior to the study LTOT 55±23 vs 18±20 p<0.005 Historical LTOT 47±25 vs 38±29 NS	Retrospective, historical controls, no patients lost to F/U
			Historical LTOT N=29 Male: 53% Age: 66	PaO_2 54± 6.8 $PaCO_2$ 51 ± 4.5	31±12	ND	18 mo 17%		

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Okubadejo 1996 UK	6 mo of therapy	Inclusion: COPD FEV_1<1.5L, PaO_2 <7.3 when stable or a PaO_2 <8.0 with evidence of cor pulmonale & ECG changes Exclusion: age <45, COPD exacerbation within past 3 wk	N=23 Male: 35% Age: 71 Median (47-82)	PaO_2 53± 6.0 $PaCO_2$ 50± 9.0	40±17	17	6 mo 17%	*Pulmonary function (n=19)* FEV_1% Predicted 38±17 *Quality of life (n=19)* SGRQ Total NS SIP NS	Baseline data for 19 survivors only, no patients lost to F/U
Heaney 1997 N Ireland	> 8 y study period	Inclusion: period 9/86-4/89, lifestyle or work severely limited, PaO_2 < 6 kPa, no smoking; period > 4/89 FEV_1 <1.51 L /FVC < 2.01, PaO_2 < 7.3 kPa, $PaCO_2$ > 6 kPa, edema, clinically stable, optimized therapy	N=178 Male: 62% Age: 64	PaO_2 49 $PaCO_2$ 49	FEV_1 L 0.93	10-15 (17%) > 15 (64%)	10 mo 31% 20 mo 50% 60 mo 67%		Ambidirectional F/U, no patients lost to F/U
Aida 1998 Japan	Ambi-directional 6 y, mean F/U 2.4 y	Inclusion: LTOT patients registered between 7/85 – 6/93, COPD, 40-80 y, PaO_2 ≤ 60 mmHg - room air at rest, O_2 > 15h/d	N=4,552 466 COPD Male*: 73% Age*: 69 *Subgroup data	PaO_2 50.3 $PaCO_2$ 49	ND	> 15	1 y 12.1% 2 y 37.9% 5 y 60.5%		1,740 institutions in registry, diagnosed by individual physician, overlapping population with Miyamoto 1995

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Zielinski 1998 Poland	6 y	Inclusion: stable hypoxemia (PaO_2 < 55) assessed at steady state PaO2=56 to 65	N=95 Male: 76% Age: 58	PaO_2 55± 6 $PaCO_2$ 48 ± 9	FEV_1 L 0.84±0.3	14	2 y 23%	"LTOT for 14 to 15h/d resulted in a long-term stabilization of pulmonary hypertension" 19 patients completed 6 years of LTOT	---
Hjalmarsen 1999b Sweden	3 mo	Inclusion: stable PaO_2≤ 7.3 kPa or ≤8.0 kPa with coexisting polycythemia or cor pulmonale Exclusion: history of cardiac or cerebro-vascular disease, history of psychiatric disorder by DSM-IV, metabolic or endocrine disorder, condition may influence cognitive performance	N=10 Male: 40% Age: 66 (51-74)	PaO_2 50±8.3 $PaCO_2$ 53±11	38±12	18-24	ND	*Neuropsychological assessment* No significant changes comparing baseline and 3 months after LTOT for the following: Trail Making Test Seashore Rhythm Test WMS-R CalCAP Grooved Pegboard STMS	No patients lost to F/U

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Farrero 2001 Spain	1 y F/U	Inclusion: primary COPD requiring LTOT, history of ≥6 mo LTOT, resides near hospital	N=62 Male: ND Age: 68	PaO_2 50±7 $PaCO_2$ 56±8	27±9	ND	1 y 34%	*Emergency room visits (n=48, change over 1 y F/U)* -1.6±2.0 *Hospital admission rate (n=48)* -1.3±1.7 *Hospital stay (n=48)* -18±25 *Quality of life (n=16)* NS for Chronic Respiratory Questionnaire *Pulmonary function* ***(n=48)*** Pre Post FEV_1 % 27±8 24±6 p=0.01	No patients lost to F/U
Sergi 2002 Basel	42 mo	Inclusion: stable PaO_2 >60, FEV_1 < 60% predicted & FEV_1/VC<70% with TLC >80% predicted Exclusion: asthma, bronchiectasis, interstitial lung, heart disease, other serious disorder, hepatic cirrhosis or chronic renal failure	N=10 Male: ND Age: 66	PaO_2 63±2.3 $PaCO_2$ 44±2.3 See comments	40±3.4	>18	ND	*Pulmonary function* FEV_1 % 34±2.2 p<0.05 Data compared to baseline, not at start of LTOT. 9 were desaturators	Of 52 enrolled, 10 developed chronic respiratory failure requiring LTOT (PaO_2<55), no ABG data reported at start of LTOT, LTOT started at 22±6.8 mo (median, 12-36 m) after enrollment
Bratel 2003 Sweden	6.2±0.9 mo F/U	Inclusion: Moderate to severe airway obstruction <70% predicted, FEV_1/VC<65%	N=12 Male: ND Age: 69 (n=19)	PaO_2 55±8 $PaCO_2$ 44±6.7	29±18	≥ 16 (n=11)	ND	*Pulmonary function* FEV_1 % 28±17 ns compared to baseline	No patients lost to F/U

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Retrospective									
McKeon 1987 Australia	14 y F/U	Inclusion: LTOT guidelines established Oct 1982: COPD, right ventricular hypertrophy, secondary polycythemia, PaO_2 < 56 mmHg & recurrent right heart failure; Prior to Oct 1982: LTOT qualification by means test	N=84 Male: ND Age: ND	ND	ND	ND	1 y 6% 2 y 20% 5 y 64%	---	Most pts already on LTOT at initiation of study, no patients lost to F/U
Corrado 1994 Italy	4 y F/U	Inclusion: COPD with chronic respiratory insufficiency admitted 1984-1986 for acute respiratory failure	N=35 Male: 74% Age: 66	PaO_2 52±5.7 $PaCO_2$ 54±6.9	24±9.9	>15 (15-18)	1 y 6% 2 y 17% 3 y 37% 4 y 49% (graph estimates)	"LTOT of more than 15h/d seems to improve survival for at least 2 to 4 years."	Baseline data at discharge, no patients lost to F/U

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Buyse 1995 Belgium	3 y F/U	Inclusion: adults with stable disease prescribed LTOT on 7/1/84 – 7/31/92	COPD N=49 Male*: 77% Age*: 62 *Multiple diseases N=83	PaO_2 50±7 $PaCO_2$ 48±10 (n=46)	33±17 Multiple diseases N=83	ND	1 y 13% 2 y 40% (n=15)	---	27% of sample had PaO_2 55-60
Miyamoto 1995 Japan	7 y	Inclusion: LTOT pts registered between 7/85 – 6/93, $PaO_2 \leq 55$ mmHg - room air at rest, or ≤ 60 w/pulmonary hypertension or severe hypoxemia (≤ 55) during exercise or sleep Exclusion: $PaO_2 > 60$ mmHg, $FEV_1/FVC > 70\%$	N=5,055 Male: 75% Age: 70	PaO_2 M 51±6.9 F 49±7.3 $PaCO_2$ M 48±10 F 51±9.4	ND	ND	1 y 13% 2 y 25% 3 y 36% 5 y 58%	*Survival* M 4.8±9.9 vs F 5.28±0.18 p<0.05 NS for length of oxygen inhalation between sexes for LTOT pts > 15 h/d, n=unknown Significant (p<.05) difference between sexes for baseline PaO_2 & $PaCO_2$ values	1,740 institutions in registry, diagnosed by individual physician, overlapping population with Aida 1998
Chailleux 1996 2003 France	10 y	Inclusion: LTOT patients $PaO_2 \leq 55$ & >15h oxygen treated 1/1984 -12/1992	N=12,403 Chronic bronchitis 1,755 Asthma 551 Emphysema 1,556 Male: 84% Age: 69	PaO_2 M 53±7.5 F 53±7.2 $PaCO_2$ M 47± 8.6 F 48± 8.3	M 35±15 F 41±18	ND	1 y 25% 2 y 41% 5 y 70% (graph estimates)	In COPD: male sex, older age, lower BMI, FEV1% predicted, PaO_2 and $PaCO_2$ are independent negative prognostic factors for survival rate. Survival is slightly better for patients with bronchitis & asthma with permanent dyspnea and worse for those with emphysema	

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Hjalmarsen 1999a Sweden	8 y F/U	Inclusion: PaO_2 ≤ 7.3 kPa, LTOT following international prescription guidelines Exclusion: Interstitial pulmonary fibrosis, cancer, left heart failure	N=76 Male: 50% Age: 67	PaO_2 48±0.75 (n=67) $PaCO_2$ 53±1.5 (n=66)	34±1.7 (n=59)	Prescribed >15	2 y 27% 5 y 50%	*Survival* 2 y 5 y M 56% 30% F 83% 60% p<0.005	1 withdrawal
Crockett 2001 Australia	10 y F/U	Inclusion: Patients with chronic airflow limitation with LTOT between 1977 and 1999 Exclusion: asthma	N=505 Male: 49% Age: 70	PaO_2 M 53± 8.1 F 50.9±8.1 $PaCO_2$ M 48±10 F 50±8.5	FEV_1 L M: 0.86±0.45 F: 0.65±0.25	Prescribed > 15 for Belgian, Prescribed mean 19 for Swedish	1 y 25% 2 y 49% 5 y 81% 10 y 99%	---	---
Ringbaek 2002 Denmark	10 mo of therapy	Inclusion: COPD hypoxaemic patients from Danish Oxygen Registery	Total N=246 COT Male: 57% Age: 68 --- NCOT Male: 49% Age: 72	PaO_2 48±5.3 $PaCO_2$ 51±9.0 --- PaO_2 48±6.8 $PaCO_2$ 49±11	30±11 (n=114)	≥15 --- < 15	ND	*Hospitalization* Post Days 23.7±24.5 13.4± 22.7 p<0.001 Admission 2.1±1.9 1.6±2.2 p<0.001 Hospital day were reduced by 23.8%, 43.5% and 31.2% Re- LTOT is associated with a reduction in hospitalization, ns between groups	---

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Demirel 2003 Turkey	17±15 mo (1-71) of therapy	Inclusion: Patients received COT COPD by ATS with ABG data	N=127 124 COPD (97%) Male: 73% Age: 62	PaO_2 52± 11 $PaCO_2$ 50±9.6	31±12	12 (11%) > 15 (43%)	5.5% F/U interval unknown	77% patients stated that they had benefited from therapy. "Continuous oxygen therapy is an effective treatment modality but patient compliance remains a problem"	ABG data analyzed for 86 patients, 6 centers, 7 lost to F/U

Evidence Table 4. Cohort studies of LTOT for COPD patients with PaO_2 between 56 and 59 mmHg

Study Year Country	Study design		Population	Baseline		O_2 therapy: hours/day	Outcomes		Comments
	Duration	Inclusion / exclusion		PaO_2 $PaCO_2$ mmHg	FEV_1 (% Predicted)		Mortality	Other outcomes	
Prospective									
Sliwinski 1992 1993 Poland	2 y of therapy	Inclusion: PaO_2 < 55 mmHg, or PaO_2 55-65 with pulmonary hypertension, right ventricular hypertrophy, elevated hematocrit Exclusion: conditions influencing survival (sys hypertension, IHD, left heart failure, liver cirrhosis, renal failure, DM, cancer	N=46 Male: 83% Age: 55	PaO_2 57±6 $PaCO_2$ 48±9	FEV_1 L 0.84±0.32	15	1 y 8.7% 2 y 33%	*Pulmonary function* FEV_1 0.7±0.3 p<0.01 (compare with baseline at 2 y, n=19)	---
Sandek 2001 Sweden	6 mo F/U	Inclusion: irreversible airflow obstruction FEV_1 %P < 70 & FEV_1/FVC ratio <70%, 2 PaO_2 measures < 7.3 kPa (3 wk apart) or 7.3-7.9 w/chronic right heart insufficiency	N=14 Male: ND Age: 69 (45-74)	PaO_2 58 (46-63) $PaCO_2$ 41 (30-49) Median	34 Median (17-68)	16	ND	*Pulmonary function* FEV_1 % 32 (14-66) Median	Data inconsistent, statistical methods used inappropriate for data, no patients lost to F/U
Retrospective									
Hjalmarsen 1999a Sweden	8 y F/U	Inclusion: PaO_2 ≥ 7.4 kPa, LTOT following international prescription guidelines Exclusion: Interstitial pulmonary fibrosis, cancer, left heart failure	N=48 Male: 79% Age: 69	PaO_2 62±0.75 $PaCO_2$ 44±1.5	33±2.0 (SE) (n=43)	Prescribed >15	24 mo 22% 60 mo 60%	*Survival* 50% survival: Male 4.2 y Female 5.1 y	1 withdrawal

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