Long-Term Oxygen Therapy for Severe COPD

June 11, 2004
Long-Term Oxygen Therapy for Severe COPD

FINAL REPORT
June 11, 2004
Tufts-New England Medical Center EPC

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

This report is based on research conducted by the Tufts-New England Medical Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0022). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decision-makers; patients and clinicians, health system leaders, and policymakers, make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.
Table of Contents

Background 3
Methods 6
Results 12
   PAO₂ ≤ 55 mmHg 15
   PaO₂ 56-59 mmHg 23
   PaO₂ 60-64 mmHg 26
   Adverse Effects 28
Conclusions 29
References 31
Appendix I. Evidence Tables
   Evidence Table 1. Randomized Controlled Trials PaO₂ ≤ 55 mmHg
   Evidence Table 2. Randomized Controlled Trials PaO₂ 60-64 mmHg
   Evidence Table 3. Cohort Studies PaO₂ ≤ 55 mmHg
   Evidence Table 4. Cohort Studies PaO₂ 56-59 mmHg
Appendix II. List of Rejected Articles
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 \( \text{PaO}_2 \leq 55 \text{ mmHg} \), or those with \( \text{PaO}_2 \) 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: \( \text{PaO}_2 \) (mmHg) \( \leq 55, 56 - 59, \) 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$_2$ ≤ 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

<table>
<thead>
<tr>
<th>Population PaO₂ mmHg</th>
<th>RCTs # studies (# patients)</th>
<th>Cohort Studies # studies (# patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ ≤ 55 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂ 56 – 59 mmHg</td>
<td>ND</td>
<td>prospective cohorts 1 (n=46) Sliwinski 1992</td>
</tr>
<tr>
<td></td>
<td>ND</td>
<td>Pulmonary function 1 (n=14) Sandek 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital admission 1 (n=46) Sliwinski 1992</td>
</tr>
<tr>
<td>Population PaO₂ mmHg</td>
<td>RCTs # studies (# patients)</td>
<td>Cohort Studies # studies (# patients)</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>60 – 64</td>
<td>2 (n=211) Gorecka 1997, Chaouat 1999</td>
<td>Pulmonary function 1 (n=76) Chaouat 1999, retrospective cohorts 1 (n=48) Hjalmarsen 1999a</td>
</tr>
</tbody>
</table>

ND – no data
HRQL – health related quality of life
Patients with $\text{PaO}_2 \leq 55$ mmHg

Two RCTs enrolled 290 COPD patients with $\text{PaO}_2 \leq 55$ 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 $\text{PaO}_2 \leq 55$ 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 $\text{PaO}_2$ of 51.5 mmHg in the NOT group and 50.8 mmHg in the COT group, mean $\text{PaCO}_2$
of 43 mmHg and % predicted FEV\textsubscript{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 PaO₂ 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 FEV₁ in men who received LTOT was slightly higher than the control (0.76 L vs. 0.65 L). Although the mean baseline PaCO₂ 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$_2$ ≤ 55 mmHg

<table>
<thead>
<tr>
<th>Study Year Country</th>
<th>Study Size</th>
<th>Study duration (years)</th>
<th>Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 y  2 y  3 y  5 y</td>
<td></td>
</tr>
<tr>
<td><strong>Prospective Cohort Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aida 1998 Japan</td>
<td>4,552</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Gorecka 1992 Poland</td>
<td>315</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Dubois 1990 1994 Belgium</td>
<td>270</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Heaney 1997 N Ireland</td>
<td>178</td>
<td>&gt; 8 (10 mo)</td>
<td>31</td>
</tr>
<tr>
<td>Dallari 1994 Italy</td>
<td>166</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Borak 1996 Poland</td>
<td>1224</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Zielinski J 1998 Poland</td>
<td>95</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Oswaldmannosser 1995 France</td>
<td>84</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>Vergeret 1989 Denmark</td>
<td>75</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Farrero 2001 Spain</td>
<td>62</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Simonds 1995 England</td>
<td>33</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Okubadejo 1996 UK</td>
<td>23</td>
<td>0.5</td>
<td>17 (6 mo)</td>
</tr>
<tr>
<td>Study Year Country</td>
<td>Study Size</td>
<td>Study duration (years)</td>
<td>Mortality %</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------</td>
<td>------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 y</td>
</tr>
<tr>
<td>Clini 1996 Italy</td>
<td>34</td>
<td>1.5</td>
<td>17-23</td>
</tr>
<tr>
<td>Ashutosh 1983 USA</td>
<td>28</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weitzenblum 1985</td>
<td>24</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1991 France</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krop 1973 Stewart</td>
<td>12</td>
<td>2</td>
<td>8.3</td>
</tr>
<tr>
<td>1975 US</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective Cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chailleux 1996</td>
<td>12,403</td>
<td>10</td>
<td>~25</td>
</tr>
<tr>
<td>2003 France</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miyamoto 1995</td>
<td>5,055</td>
<td>7</td>
<td>~13</td>
</tr>
<tr>
<td>Crockett 2001</td>
<td>505</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demirel 2003</td>
<td>127</td>
<td>1.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Turkey</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McKeon 1987</td>
<td>84</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrado 1994</td>
<td>35</td>
<td>4</td>
<td>~6</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hjalmarsen 1999a</td>
<td>76</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>Sweden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buyse 1995</td>
<td>15</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Belgium</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
Long-term oxygen therapy for COPD

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 the 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 \( \text{PaO}_2 \leq 55 \) 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$_2$ ≤ 55 mmHg and PaO$_2$ ≥ 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$_2$ ≤ 55 group, and 78% and 40% in the PaO$_2$ ≥ 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 \( \text{PaO}_2 \leq 55 \text{ mmHg} \). Only 2 RCTs published over 20 years ago evaluated patients with \( \text{PaO}_2 \) between 56 and 59 mmHg. Both of these trials reported similar reduction of overall mortality. Two RCTs conducted in patients with \( \text{PaO}_2 \) 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 \( \text{PaO}_2 \leq 55 \). 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 \( \text{PaO}_2 \leq 55 \text{ mmHg} \) 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.
REFERENCES


Petty TL, Bliss PL. Ambulatory oxygen therapy, exercise, and survival with advanced chronic obstructive pulmonary disease (the Nocturnal Oxygen Therapy Trial revisited). Respir Care 2000;45:204-11.


Long-term Oxygen Therapy for COPD

Evidence Tables

Evidence Table 1. PaO$_2$ $\leq$ 55 mmHg Randomized Controlled Trials

  PaO$_2$ 56-59 mmHg – No Randomized Controlled Trials

Evidence Table 2. PaO$_2$ 60-64 mmHg Randomized Controlled Trials

Evidence Table 3. PaO$_2$ $\leq$ 55 mmHg Cohort Studies

Evidence Table 4. PaO$_2$ 56-59 mmHg Cohort Studies

  PaO$_2$ 60-64 mmHg – No Cohort Studies
## Evidence Table 1. Randomized controlled trials of LTOT for COPD patients with PaO$_2$ ≤55 mmHg

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Country</th>
<th>Study design</th>
<th>Population</th>
<th>Baseline</th>
<th>O$_2$ therapy hrs/day</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 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 | 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 |
| NOTT 1980 | 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 | PaO$_2$: 52±1.3 PaCO$_2$: 44±1.5 SE | COT 30  
12 mo COT  
PaO$_2$: 51  
PaCO$_2$: 43 | COT 18±4.8  
24 mo COT  
PaO$_2$: 52 PaCO$_2$: 44 | 12 mo COT  
FEV$_1$: 12±3.2 (SE)  
NOT  
21%±4.0 (SE) odds ratio 0.53 (0.25-1.11)  
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. |
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Country</th>
<th>Duration; RCT features</th>
<th>Study design</th>
<th>Population</th>
<th>Baseline</th>
<th>O₂ therapy hrs/day</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC 1981 UK</td>
<td>UK</td>
<td>5 y F/U; table of random numbers, unblinded</td>
<td>Inclusion: &lt;70, chronic bronchitis or emphysema with FEV₁ &lt;1.2L, PaO₂ 40-60 mmHg; Exclusion: fibrotic or infiltrative lung disorder, pneumoconiosis, severe kyphoscoliosis, pulmonary embolism, elevated BP, coronary arterial or other life-threatening disease</td>
<td>N=87</td>
<td>PaO₂ 51 PaCO₂ 54</td>
<td>FEV₁ L &gt;0.6 W &gt;0.7 M</td>
<td>&gt;15</td>
<td>5 years Treatment: 45% Control: 67% OR 0.42 (0.18, 0.98)</td>
</tr>
<tr>
<td>Cuvelier 2002 France</td>
<td>France</td>
<td>ND; Cross-over, double dummy, single-blind</td>
<td>Inclusion: stable COPD, LTOT at home, able to perform walking tests</td>
<td>N=10 Male: 90% Age: 65</td>
<td>PaO₂ 55± 6.3 PaCO₂ 46± 7.4</td>
<td>98± 27</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Country</th>
<th>Duration / RCT features</th>
<th>Study design</th>
<th>Population</th>
<th>Baseline</th>
<th>O₂ therapy hours/day</th>
<th>Outcomes</th>
<th>Other outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Poland</td>
<td>7 y F/U, mean 41 mo; Computer central generated random numbers, not blinded</td>
<td>Inclusion: single diagnosis COPD, 40-80 y with airway limitation (FEV₁/VC post bronchodilator of &lt;70%, PaO₂ 56-65 from 1987-92, F/U through 1994</td>
<td>N=135 Male: 76% Age: 61</td>
<td>PaO₂ 60±2.8 PaCO₂ 44±6.7</td>
<td>30±9.8</td>
<td>14</td>
<td>LTOT 56% Control 49% Odds Ratio (all-cause) 1.4 (0.70–2.7)</td>
<td>9 regional LTOT centers, no patients lost to F/U</td>
</tr>
<tr>
<td>1999</td>
<td>Europe</td>
<td>35 mo F/U Table of random sampling numbers, NOT to even numbers, control to odd numbers, unblinded</td>
<td>Inclusion: FEV₁/VC ratio &lt;60% predicted value, 2 PaO₂ measures 56-69 (4 weeks apart), PaCO₂ ≥45, nocturnal desaturation ≥ 30% &amp; SaO₂ &lt; 90%</td>
<td>N=76 Male: ND Age: 63 NOT 41 No NOT control: 35</td>
<td>PaO₂ 63±3.3 PaCO₂ 45±5.6</td>
<td>39±16</td>
<td>NOT 8.9±1.9 NOT 22% Control 20% Odds Ratio 1.1 (0.37-3.4)</td>
<td>There was no significant change in pulmonary volumes, FEV₁ and resting and exercising PAP</td>
<td>12 NOT &amp; 10 controls received LTOT due to fall in PaO₂ levels, mortality analyses on intention to treat, similar results if LTOT exposure removed, 6 outpatient centers, 11 withdrawals, 2 lost to F/U</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Cohort studies of LTOT for COPD patients with PaO₂ ≤55 mmHg

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Country</th>
<th>Study design</th>
<th>Population</th>
<th>Baseline</th>
<th>O₂ therapy: hours/day</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prospective</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krop 1973</td>
<td>US</td>
<td>25.2 mo F/U (4 - 40)</td>
<td>Inclusion: COPD, PaO₂ &lt; 55 mmHg under optimal therapy, additional PaO₂ decrease with treadmill exercise, relief of hypoxemia with 2 L/min O₂ therapy</td>
<td>N=12 Male: 100% Age: 55 (33-64)</td>
<td>PaO₂ 49±5.0 PaCO₂ 44±6.9</td>
<td>FEV₁ L 0.68±0.15</td>
<td>24</td>
</tr>
<tr>
<td>Stewart 1975</td>
<td>US</td>
<td>25.2 mo F/U (4 - 40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Outcomes**:
- **Survival**: 56% at 2½ y
- **Pulmonary function** (n=11): NS for PaCO₂, FVC, FEV₁
- **Hospital days**: ~30 days/patient before LTOT (n=11) ~20 days/patient 1 year after LTOT (n=10)
- **Quality of life at 1 month**
  - WAIS or W-B: —— Post
    - 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
    - BHP: 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
<table>
<thead>
<tr>
<th>Study Year Country</th>
<th>Study design</th>
<th>Population</th>
<th>Baseline</th>
<th>O₂ therapy: hours/day</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Ashutosh 1983 USA  | 2 y F/U     | Inclusion: FEV₁ < 2 SD predicted value and FEV₁/FVC% < 70%, right heart failure, mean PAP > 20 mmHg, pulmonary capillary wedge pressure < 15 mmHg | Responders PAP: 37±12  
N=17  
Male: ND  
Age: 57  
PaO₂: 53±8  
PaCO₂: 46±9 | Responders PAP: 37±12  
N=17  
Male: ND  
Age: 57  
PaO₂: 53±8  
PaCO₂: 46±9 | Prescribed > 18 | Mortality | Survival |
|                    |             | Exclusion: left ventricular disease | Non-responders PAP: 33±12  
N=11  
Male: ND  
Age: 60  
PaO₂: 54±12  
PaCO₂: 46±10 | Prescribed > 18 | Other outcomes | Significant for responders (reduction in pulmonary hypertension) over non-responders, p<0.005 |
<p>|                    |             |            |          |                      |          |          | Significant change of PAP &gt; or &lt; 5 mmHg while breathing 28% O₂ for 24 h used to divide patients into 2 groups; 1 withdrawal | 2 withdrawals |</p>
<table>
<thead>
<tr>
<th>Study Year Country</th>
<th>Study design</th>
<th>Population</th>
<th>Baseline</th>
<th>O2 therapy: hours/day</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weitzenblum 1985 1991 France</td>
<td>Duration: 11.5 y F/U, 44±30 mo of therapy (12-120)</td>
<td>Inclusion: history of chronic bronchitis, airflow obstruction &lt; 1.5 L, hypoxemia &amp; PaO₂ &lt; 60 mmHg &amp; clinically stable at 3 monthly measures, right heart failure or right ventricular hypertrophy, Ppa&gt;20 mmHg, ≥ 1 y between catheterization before &amp; after onset of LTOT, compliance (&gt;15 h/d)</td>
<td>N=24 Male: 92% Age: 59 (41-74)</td>
<td>PaO₂ 52±6.5 PaCO₂ 49±8.2</td>
<td>Mortality: 33 mo 25%* 73 mo 54%</td>
<td>Hospital days per year (n=16)  Pre-LTOT 18±16 Post-LTOT 9±19 0.10 &gt; p &gt; 0.05 (NS)</td>
</tr>
<tr>
<td></td>
<td>Inclusion / exclusion</td>
<td></td>
<td></td>
<td></td>
<td>Other outcomes: Pulmonary function  FEV₁ % 33±13 NS (compared with baseline)</td>
<td>Pulmonary arterial hypertension  Pre-LTOT 27±9.1 Post-LTOT 24±7.1 ns (compared to baseline)</td>
</tr>
<tr>
<td>Study Year</td>
<td>Study Country</td>
<td>Study design</td>
<td>Population</td>
<td>Baseline</td>
<td>O₂ therapy: hours/day</td>
<td>Outcomes</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>--------------</td>
<td>------------</td>
<td>----------</td>
<td>-----------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Vergeret</td>
<td>1989 Denmark</td>
<td>Inclusion: 40-75 y, severe COPD FEV₁/FVC&lt;60%, total lung capacity &gt;80% of reference values, FEV₁&lt;1L &amp; stable chronic respiratory insufficiency PaO₂ &lt;8kPa &amp; &gt;5.3kPa PaCO₂ &lt;8.2kPa Exclusion: pts on portable O₂, &gt;3 admissions</td>
<td>Fixed O₂ N=75 Male: 84% Age: 63</td>
<td>PaO₂ 54±7.5 PaCO₂ ND</td>
<td>14</td>
<td>1 y 12% No significant clinical and functional differences between 2 groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Portable O₂ N=84 Male: 90% Age: 61</td>
<td>PaO₂ 49±6.7 PaCO₂ 46±14</td>
<td>17</td>
<td>1 y 18%</td>
</tr>
<tr>
<td>Lahdensuo</td>
<td>1989 Finland</td>
<td>Inclusion: severe COPD, stable disease, PaO₂&lt;55 or 55-59 &amp; hematocrit &gt; 55, cor pulmonale, or history of ≥1 acute cardiac failure from cor pulmonale Exclusion: smoking in the past 3 mo</td>
<td>N=26 Male: 73% Age: 63</td>
<td>PaO₂ 49±6.7 PaCO₂ 46±14</td>
<td>Prescribed 24</td>
<td>ND</td>
</tr>
</tbody>
</table>

---

8 withdrawals

5 withdrawals
<table>
<thead>
<tr>
<th>Study Year Country</th>
<th>Study design</th>
<th>Population</th>
<th>Baseline</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duration</td>
<td>Inclusion / exclusion</td>
<td>N=270</td>
<td>PaO₂</td>
<td>PaCO₂</td>
</tr>
<tr>
<td>Dubois 1990 1994 Belgium</td>
<td>6 y</td>
<td><strong>Inclusion:</strong> PaO₂ &lt;55 in controlled steady state ≥3 wks, PaCO₂ did not increase “excessively”  <strong>Exclusion:</strong> A severe disease that might be expected to influence short-term mortality. No patients had previous LTOT</td>
<td>Male: 86% Age: 66</td>
<td>PaO₂ 48±6 PaCO₂ 47±9</td>
<td>30±12</td>
</tr>
<tr>
<td>Strom 1991 1993 1998 Sweden</td>
<td>28 mo F/U (15-45)</td>
<td><strong>Inclusion:</strong> Stable adults treated for chronic hypoxemia w/LTOT, approx 7.5 kPa, resting &gt; 8 kPa, registered 1/1/87 – 6/30/89</td>
<td>Male: 50% Age: 67</td>
<td>PaO₂ 50 PaCO₂ 49</td>
<td>27±15</td>
</tr>
<tr>
<td>Study Year</td>
<td>Study Country</td>
<td>Study design</td>
<td>Population</td>
<td>Baseline</td>
<td>O2 therapy: hours/day</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>--------------</td>
<td>------------</td>
<td>----------</td>
<td>----------------------</td>
</tr>
<tr>
<td>1992 Poland</td>
<td>Study design</td>
<td>Duration: 1 y F/U</td>
<td>Inclusion: PaO₂ ≤55 or 56-65 if one of following is present: Hct ≥55%, radiological signs of pulmonary arterial hypertension, ECG signs of right ventricular hypertrophy</td>
<td>N=315 Male: 74% Age: 62</td>
<td>PaO₂ 51±8 PaCO₂ 51±11</td>
</tr>
<tr>
<td>1994 Italy</td>
<td>Study design</td>
<td>Duration: 24 mo F/U (2-50)</td>
<td>Inclusion: COPD on LTOT from 1987-1992</td>
<td>N=166 Male: ND Age: 69</td>
<td>PaO₂ 54±5.8 PaCO₂ 51±7.6</td>
</tr>
<tr>
<td>1995 England</td>
<td>Study design</td>
<td>Duration: 1.6 y median for NIPPV (0.1-6.3) 5 y F/U</td>
<td>Inclusion: symptomatic, chronic hypercapnic respiratory failure unresponsive to O₂ therapy, progressive deterioration in symptoms &amp; arterial blood gas tensions</td>
<td>N=180 33 COPD Male: ND Age*: 57 *Subgroup data</td>
<td>PaO₂ 46±6.0 PaCO₂ 62±14</td>
</tr>
<tr>
<td>Study Year</td>
<td>Country</td>
<td>Study design</td>
<td>Duration</td>
<td>Inclusion / exclusion</td>
<td>Population</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>--------------</td>
<td>----------</td>
<td>-----------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Oswaldmannosser 1995 France</td>
<td>5 y (1-12 F/U)</td>
<td>Inclusion: COPD, FEV1/VC ratio &lt; 60%, TLC &gt; 80% of predicted value Exclusion: Lung disease, (sequela of pulmonary tuberculosis, pneumoconiosis), left heart disease, obesity (BMI &gt; 32), sleep apnea, or other severe disease</td>
<td>N=84 Male: 89% Age: 63</td>
<td>PaO2 52±5.4 PaCO2 45±7.6</td>
<td>FEV1 L 0.8 (0.3)</td>
</tr>
</tbody>
</table>
| Borak 1996 Poland | 1 y F/U | Inclusion: PaO2 < 55 mmHg, or 55-65 if polycythemtic | N=124 Male 68% Age: 56 (28-76) | PaO2 55±6.2 PaCO2 47±8.2 | FEV1 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 Genera I 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
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Country</th>
<th>Study design</th>
<th>Duration</th>
<th>Inclusion / exclusion</th>
<th>Population</th>
<th>Baseline</th>
<th>O₂ therapy: hours/day</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin 1996</td>
<td>Taiwan</td>
<td>Inclusion: stable hypercapnia, PaO₂≥44 mmHg, FEV₁&lt;70%, FEV₁/FVC&lt;70%, FEV₁/FVC&lt;50% predicted, PaO₂&lt;55 mmHg, or PaO₂&gt;55-60 right heart failure &amp; polycythemia Exclusion: sleep apnea with hypopnea index ≥10, &gt;15% increase in FEV₁, CNS, neuromuscular, CHF, endocrine, renal, or unstable disorders &lt; 1 mo</td>
<td>2 weeks of therapy</td>
<td>N=12 Male: 58% Age: 65</td>
<td>PaO₂ 52±2.5 PaCO₂ 51±3.5</td>
<td>ND</td>
<td>24</td>
<td>Mortality Other outcomes</td>
<td></td>
</tr>
<tr>
<td>Clin 1996</td>
<td>Italy</td>
<td>Inclusion: COPD on LTOT ≥ 18 months, chronic hypercapnia, PaCO₂&gt;50, ≥ one hospital admission due to severe exacerbation in past 18 months Exclusion: ≥ 15% increase FEV₁</td>
<td>18 mo of therapy</td>
<td>LTOT N=17 Male: 53% Age: 67</td>
<td>PaO₂ 50±4.5 PaCO₂ 48±6.8</td>
<td>33±10</td>
<td>&gt;8 nightly</td>
<td>18 mo 18%</td>
<td></td>
</tr>
</tbody>
</table>

Pulmonary function at 18 months
FEV₁ % (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

No patients lost to F/U

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

Retrospective, historical controls, no patients lost to F/U
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Country</th>
<th>Study design</th>
<th>Population</th>
<th>Baseline</th>
<th>O2 therapy: hours/day</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okubadejo 1996 UK</td>
<td></td>
<td>Inclusion: COPD FEV1&lt;1.5L, PaO2&lt;7.3 when stable or a PaO2 &lt;6.0 with evidence of cor pulmonale &amp; ECG changes Exclusion: age &lt;45, COPD exacerbation within past 3 wk</td>
<td>N=23 Male: 35% Age: 71 Median (47-82)</td>
<td>PaO2 53± 6.0 PaCO2 50± 9.0</td>
<td>40±17</td>
<td>17</td>
<td>6 mo 17% Pulmonary function (n=19) FEV1 % Predicted 38±17 Quality of life (n=19) SGRQ Total NS SIP NS</td>
</tr>
<tr>
<td>Heaney 1997 N Ireland</td>
<td>&gt; 8 y study period</td>
<td>Inclusion: period 9/86-4/89, lifestyle or work severely limited, PaO2 &lt; 6 kPa, no smoking; period &gt; 4/89 FEV1 &lt;1.51 L FVC &lt; 2.01, PaO2 &lt; 7.3 kPa, PaCO2 &gt; 6 kPa, edema, clinically stable, optimized therapy</td>
<td>N=178 Male: 62% Age: 64</td>
<td>PaO2 49 PaCO2 49</td>
<td>FEV1 L 0.93</td>
<td>10-15 (17%) &gt; 15 (64%)</td>
<td>10 mo 31% 20 mo 50% 60 mo 67%</td>
</tr>
<tr>
<td>Aida 1998 Japan</td>
<td>Ambidirectional 6 y, mean F/U 2.4 y</td>
<td>Inclusion: LTOT patients registered between 7/85 – 6/93, COPD, 40-80 y, PaO2 ≤ 60 mmHg - room air at rest, O2 &gt; 15h/d</td>
<td>N=4,552 466 COPD Male*: 73% Age*: 69 *Subgroup data</td>
<td>PaO2 50.3 PaCO2 49</td>
<td>ND</td>
<td>&gt; 15</td>
<td>1 y 12.1% 2 y 37.9% 5 y 60.5%</td>
</tr>
<tr>
<td>Study Year</td>
<td>Study Country</td>
<td>Duration</td>
<td>Study design</td>
<td>Population</td>
<td>Baseline</td>
<td>O₂ therapy: hours/day</td>
<td>Outcomes</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>----------</td>
<td>--------------</td>
<td>------------</td>
<td>----------</td>
<td>----------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Zielinski 1998 Poland</td>
<td>6 y</td>
<td>Inclusion: stable hypoxemia (PaO₂ &lt; 55) assessed at steady state PaO₂=56 to 65</td>
<td>N=95 Male: 76% Age: 58</td>
<td></td>
<td>PaO₂:  55± 6 PaCO₂: 48 ± 9</td>
<td>FEV₁: 0.8±0.3</td>
<td>14</td>
</tr>
<tr>
<td>Hjalmarsen 1999b Sweden</td>
<td>3 mo</td>
<td>Inclusion: stable PaO₂≤ 7.3 kPa or ≤8.0 kPa with coexisting polycythemia or cor pulmonale</td>
<td>N=10 Male: 40% Age: 66 (51-74)</td>
<td></td>
<td>PaO₂: 50±8.3 PaCO₂: 53±11</td>
<td>38±12</td>
<td>18-24</td>
</tr>
<tr>
<td>Study Year Country</td>
<td>Study design</td>
<td>Population</td>
<td>Baseline</td>
<td>$O_2$ therapy: hours/day</td>
<td>Outcomes</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------</td>
<td>------------</td>
<td>----------</td>
<td>-------------------------</td>
<td>----------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Farrero 2001 Spain</td>
<td>1 y F/U</td>
<td>Inclusion: primary COPD requiring LTOT, history of $\geq 6$ mo LTOT, resides near hospital</td>
<td>N=62 Male: ND Age: 68</td>
<td>PaO$_2$ 50±7 PaCO$_2$ 56±8</td>
<td>27±9</td>
<td>ND 1 y 34%</td>
<td></td>
</tr>
<tr>
<td>Sergi 2002 Basel</td>
<td>42 mo</td>
<td>Inclusion: stable PaO$_2$$&gt;60$, FEV$_1$ &lt; 60% predicted &amp; FEV$_1$/VC&lt;70% with TLC &gt;80% predicted Exclusion: asthma, bronchiectasis, interstitial lung, heart disease, other serious disorder, hepatic cirrhosis or chronic renal failure</td>
<td>N=10 Male: ND Age: 66</td>
<td>PaO$_2$ 63±2.3 PaCO$_2$ 44±2.3</td>
<td>40±3.4 &gt;18 ND</td>
<td>Pulmonary function FEV$_1$ % 34±2.2 p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Bratel 2003 Sweden</td>
<td>6.2±0.9 mo F/U</td>
<td>Inclusion: Moderate to severe airway obstruction &lt;70% predicted, FEV$_1$/VC&lt;65%</td>
<td>N=12 Male: ND Age: 69 (n=19)</td>
<td>PaO$_2$ 57±8 PaCO$_2$ 44±6.7</td>
<td>29±18 $\geq 16$ (n=11)</td>
<td>Pulmonary function FEV$_1$ % 28±17 ns compared to baseline</td>
<td></td>
</tr>
</tbody>
</table>

No patients lost to F/U
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
No patients lost to F/U
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Country</th>
<th>Study design</th>
<th>Population</th>
<th>Baseline</th>
<th>O₂ therapy: hours/day</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PaO₂</td>
<td>PaCO₂</td>
<td>FEV₁</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mmHg</td>
<td>mmHg</td>
<td>(Predicted)</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McKeon 1987</td>
<td>Australia</td>
<td>14 y F/U</td>
<td>Inclusion: LTOT guidelines established Oct 1982: COPD, right ventricular hypertrophy, secondary polycythemia, PaO₂ &lt; 56 mmHg &amp; recurrent right heart failure; Prior to Oct 1982: LTOT qualification by means test</td>
<td>N=84 Male: ND Age: ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrado 1994</td>
<td>Italy</td>
<td>4 y F/U</td>
<td>Inclusion: COPD with chronic respiratory insufficiency admitted 1984-1986 for acute respiratory failure</td>
<td>N=35 Male: 74% Age: 66</td>
<td>PaO₂ 52±5.7</td>
<td>PaCO₂ 54±6.9</td>
<td>&gt;15 (15-18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Year</td>
<td>Study design</td>
<td>Duration</td>
<td>Inclusion / exclusion</td>
<td>Population</td>
<td>Baseline</td>
<td>O2 therapy: hours/day</td>
<td>Outcomes</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
<td>----------</td>
<td>----------------------</td>
<td>------------</td>
<td>----------</td>
<td>----------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Buyse 1995 Belgium</td>
<td><strong>Inclusion:</strong> adults with stable disease prescribed LTOT on 7/1/84 – 7/31/92</td>
<td>3 y F/U</td>
<td>COPD N=49 Male*: 77% Age*: 62</td>
<td>PaO2: 50±7, PaCO2: 48±10 (n=46)</td>
<td>33±17</td>
<td>ND</td>
<td>1 y 13% 2 y 40% (n=15)</td>
</tr>
<tr>
<td>Miyamoto 1995 Japan</td>
<td><strong>Inclusion:</strong> LTOT pts registered between 7/85 – 6/93, PaO2 ≤ 55 mmHg - room air at rest, or ≤ 60 w/pulmonary hypertension or severe hypoxemia (≤ 55) during exercise or sleep</td>
<td>7 y</td>
<td>N=5,055 Male: 75% Age: 70</td>
<td>PaO2: 51±6.9, F 49±7.3, PaCO2: M 48±10 F 51±9.4</td>
<td>ND</td>
<td>ND</td>
<td>1 y 13% 2 y 25% 3 y 36% 5 y 58%</td>
</tr>
<tr>
<td>Chailleux 1996 2003 France</td>
<td><strong>Inclusion:</strong> LTOT patients PaO2 ≤ 55 &amp; &gt;15h oxygen treated 1/1984 -12/1992</td>
<td>10 y</td>
<td>N=12,403 Chronic bronchitis 1,755 Asthma 551 Emphysema 1,556 Male: 84% Age: 69</td>
<td>PaO2: 53±7.5 F 53±7.1, PaCO2: M 47± 8.6 F 48± 8.3</td>
<td>M 35±15 F 41±18</td>
<td>ND</td>
<td>1 y 25% 2 y 41% 5 y 70% (graph estimates)</td>
</tr>
<tr>
<td>Study Year</td>
<td>Study Country</td>
<td>Study design</td>
<td>Duration</td>
<td>Inclusion / exclusion</td>
<td>Population</td>
<td>Baseline</td>
<td>O2 therapy: hours/day</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>--------------</td>
<td>----------</td>
<td>-----------------------</td>
<td>------------</td>
<td>----------</td>
<td>----------------------</td>
</tr>
</tbody>
</table>
| 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) | Prescribed >15 | 2 y 27%  
5 y 50% | 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$_2$: 53±8.1  
PaCO$_2$: 50.9±8.1  
M 48±10  
F 50±8.5 | Prescribed >15 for Belgian, 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 Registry | Total N=248  
COT Male: 57%  
Age: 68  
NCO1 Male: 49%  
Age: 72 | PaO$_2$: 48±5.3  
PaCO$_2$: 51±9.0  
M 48±6.8  
PaCO$_2$: 49±11 | ≥15 | ND | LTOT is associated with a reduction in hospitalization, ns between groups | --- |
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Country</th>
<th>Duration</th>
<th>Inclusion / exclusion</th>
<th>Population</th>
<th>Baseline</th>
<th>O₂ therapy: hours/day</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demirel 2003</td>
<td>Turkey</td>
<td>17±15 mo (1-71) of therapy</td>
<td>Inclusion: Patients received COT COPD by ATS with ABG data</td>
<td>N=127 124 COPD (97%) Male: 73% Age: 62</td>
<td>PaO₂ 52± 11 PaCO₂ 50±9.6</td>
<td>31±12</td>
<td>12 (11%) &lt; 15 (43%)</td>
<td>5.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ABG data analyzed for 86 patients, 6 centers, 7 lost to F/U</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Cohort studies of LTOT for COPD patients with PaO₂ between 56 and 59 mmHg

<table>
<thead>
<tr>
<th>Study Year Country</th>
<th>Study design</th>
<th>Population</th>
<th>Baseline</th>
<th>O₂ therapy: hours/day</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Sliwinski 1992 Poland | 2 y of therapy | **Inclusion:** PaO₂ < 55 mmHg, or PaO₂ 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  
PaO₂ 57±6  
PaCO₂ 48±9  
FEV₁ 0.84±0.32 | 15 | 1 y 8.7%  
2 y 33%  
Pulmonary function  
FEV₁ 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 FEV₁ %P < 70 & FEV₁/FVC ratio <70%, 2 PaO₂ 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)  
PaO₂ 58 (46-63)  
PaCO₂ 41 (30-49)  
Median | 16 | ND  
Pulmonary function  
FEV₁ % 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:** PaO₂ ≥ 7.4 kPa, LTOT following international prescription guidelines  
**Exclusion:** Interstitial pulmonary fibrosis, cancer, left heart failure | N=48 Male: 79%  
Age: 69  
PaO₂ 62±0.75  
PaCO₂ 44±1.5 | 33±2.0 (SE) (n=43) | 24 mo 22%  
60 mo 60%  
Survival  
50% survival:  
Male  4.2 y  
Female  5.1 y | 1 withdrawal |
Reject List


ventilation in patients with severe COPD.[see comment]. Chest 2000; 118(6):1582-1590. **Not population of interest, Not LTOT**


35. Estopa RM, Monasterio C, Escarrabill J. Daily life desaturations in COPD patients on LTOT: International Oxygen Club multicentre


42. Fletcher EC, Donner CF, Midgren B, Zielinski J, LeviValensi P, Braghiroli A et al. Survival in COPD patients with a daytime PaO2 greater than 60 mm Hg with and without nocturnal oxyhemoglobin desaturation. *Chest* 1992; 101(3):649-655. **Data not stratified by tx / non Tx groups**


52. Hjalmarsen A, Aasebo U, Aleksandersen G, Jorde R. Cardiovascular responses to tests for autonomic dysfunction in patients with chronic obstructive pulmonary disease with and without continuous long-term


57. Ibanez M, Aguilar JJ, Maderal MA, Prats E, Farrero E, Font A et al. Sexuality in chronic respiratory failure: coincidences and divergences between patient and primary caregiver. *Respiratory Medicine* 2001; 95(12):975-979. **No baseline data**


60. Kampelmacher MJ, van Kestern RG, Alsbach GP, Melissant CF, Wynne HJ, Douze JM et al. Characteristics and complaints of
patients prescribed long-term oxygen therapy in The Netherlands. \textit{Respiratory Medicine} 1998; 92(1):70-75. \textbf{Not population of interest}


Not LTOT


73. McDermott SC. Use of a wheelchair oxygen walker in exercise and rehabilitation of patients with chronic obstructive pulmonary disease. Respiratory Care 1977; 22(11):1222-1225. Not LTOT


75. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. American Journal of Respiratory & Critical Care Medicine 1995; 152(2):538-544. Primary to evaluate nPPV, pts had LTOT at baseline


80. O'Donohue WJ, Jr. Effect of oxygen therapy on increasing arterial oxygen tension in hypoxemic patients with stable chronic obstructive pulmonary disease while breathing ambient air. Chest 1991; 100(4):968-972. No outcomes of interest

81. Oba Y, Salzman GA, Willsie SK. Reevaluation of continuous oxygen therapy after initial prescription in patients with chronic obstructive pulmonary disease.[see comment]. Respiratory Care 2000; 45(4):401-406. No outcomes of interest


103. Soffer M, Tashkin DP, Shapiro BJ, Littner M, Harvey E, Farr S. Conservation of oxygen supply using a reservoir nasal cannula in
hypoxemic patients at rest and during exercise. *Chest* 1985; 88(5):663-668. **No outcomes of interest**


