

Long-Term Oxygen Therapy in Patients With Chronic Obstructive Pulmonary Disease and Moderate Hypoxemia

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Chronic obstructive pulmonary disease (COPD) is an irreversible lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing.¹ It affects roughly 14% of the male and 7% of the female population globally,² and it is the third-leading cause of death in the United States.³ The cost of COPD in the United States was projected to be \$50 billion in 2010.⁴ Among patients with COPD in the United States, approximately 800,000 receive long-term oxygen therapy (LTOT).⁵ Long-term oxygen therapy has been widely accepted as a means to lower the mortality rate in patients with COPD, particularly in patients with severe hypoxemia.⁶ However, the mortality benefit of this therapy in patients with COPD with mild to moderate hypoxemia is unclear, with limited evidence for its use in the literature.^{7,8}

In this review, we analyzed the available data and addressed the clinical question of whether LTOT increases the survival rate of patients with stable COPD and moderate hypoxemia. For the purposes of this review, moderate hypoxemia is defined as a P_{O_2} value of 56 to 59 mm Hg or oxygen saturation as measured by pulse oximetry (Sp_{O_2}) of 88% to 90%, with the ability to concurrently maintain oxygen saturations greater than 80% on a 6-minute walk test and 88% at rest.⁹

Clinical Question: Should long-term oxygen therapy (LTOT) be provided to patients with stable chronic obstructive pulmonary disease (COPD) who have moderate hypoxemia?

Evidence: Despite existing guidelines recommending LTOT for all patients with COPD and hypoxemia, a decreased mortality rate in patients with COPD and mild or moderate hypoxemia who receive LTOT has not been routinely demonstrated.

Recommendation: Physicians should prescribe LTOT on an individual basis in accordance with patients' symptoms.

Summary of the Evidence

The notion that LTOT improves the mortality rate in patients with COPD is derived from studies published in the 1980s, such as the Nocturnal Oxygen Therapy Trial.⁹ This study demonstrated that in patients with COPD and chronic, severe hypoxemia, continuous LTOT significantly reduced mortality and improved hematocrit levels and pulmonary vascular resistance when compared with nocturnal oxygen therapy alone.⁹ This study was followed by the British Medical Research Council Hypoxemia Trial,⁶ which further demonstrated a reduction in mortality in patients with COPD who received LTOT for more than 15 hours per day compared with no oxygen therapy (room air).⁶ However, the decrease in mortality rates of patients with mild or moderate hypoxemia who received LTOT has not been routinely demonstrated in subsequent studies.^{7,8}

Supplemental LTOT became the standard of care for patients with COPD with severe hypoxemia, but its utility in the context of mild to moderate hypoxemia is unclear.^{10,11} An end point that may explain the widespread use of LTOT to prevent adverse events is the potential symptomatic benefit of supplemental oxygen in patients with dyspnea. A meta-analysis by Ekström et al¹² aimed to assess how the use of LTOT affects breathlessness and health-related quality of life in patients with COPD and mild to moderate hypoxemia. The results showed that breathlessness could be improved with LTOT, but only when breathlessness was related to exercise and not to daily activities. This study¹² also found that LTOT had no effect on health-related quality of life.

In 2016, a parallel-group, randomized, nonblinded clinical trial across 47 university-affiliated ambulatory medical centers in the United States attempted to assess the benefit of LTOT in patients with COPD with moderate hypoxemia.¹³ Seven hundred thirty-eight stable patients with COPD with moderate hypoxemia were randomly assigned to 2 groups: one group received LTOT (n=368) and the other did not (n=370). Among the patients who received LTOT, patients with moderate resting desaturation (SpO_2 89%-93%; n=220) received 24-hour oxygen (2 L O_2 via nasal cannula), and patients with moderate exercise desaturation (SpO_2 <90% for ≥ 10 seconds and $\geq 80\%$ for ≥ 5 minutes; n=148) received oxygen only during exercise and sleep. After a 6-year follow-up, with a median follow-up of 18.4 months, the time to first hospitalization or to death did not differ between the groups (hazard ratio, 0.95; 95% CI, 0.79-1.12; $P=.52$). No difference was found in secondary outcome measures, including quality of life and breathlessness. However, factors regarding the design and methods of this study¹³ may have contributed to the nonsignificant outcome.^{14,15}

One factor is that the study design had to be modified to gain sufficient recruitment of patients, which may have led to a selection bias because sicker patients may have been excluded. Additionally, the study investigators

were not blinded, which may have introduced an observer bias in the patients and the clinicians. There were also concerns¹⁵ that patients who were smokers may have been noncompliant with remaining abstinent from smoking or that differences in smoking during times not receiving oxygen may have affected the results of the study. Additionally, the patients in the LTOT group had a lower risk of death than those in the nonsupplemental oxygen group, which would introduce a sampling bias in that both groups' baseline COPD severity and risk of death would be different. This factor may have affected the outcome, demonstrating a smaller benefit for the supplemental oxygen group. In future studies, it would be helpful to have objective evidence (whether smokers abstain from smoking during the study), perhaps by measuring serum or urinary nicotine levels and also to account for the smoking status of all participants. Moreover, none of the previous studies^{6-10,13} mentioned the hazards of smoking while using LTOT, which might be worthwhile in future clinical trials.

Discussion

With limited data demonstrating the benefit of LTOT for patients with COPD with mild to moderate hypoxemia, it is unclear that there is a definite clinical benefit of LTOT in this patient population. The Long-term Oxygen Treatment Trial¹³ is the largest trial to date regarding the use of LTOT in patients with COPD with moderate hypoxemia, and results did not show a significant clinical benefit for LTOT in this patient population.

Collectively, it appears that in stable patients with COPD with mild to moderate hypoxemia, supplemental LTOT does not prolong life or decrease the risk of hospitalization. Oxygen therapy may improve symptoms of breathlessness in some patients, but based on a validated scale used in the meta-analysis by Ekström et al,¹² there is no clear statistically significant evidence of an improvement in their quality of life. However, it is unclear whether the lack of benefit in the studies' outcome measures would have any effect on quality of life, which would be difficult to measure on a validated symptom scale. At present, the American Thoracic Society, the American College of

Chest Physicians, and the European Respiratory Society have yet to take a stance on the utility of LTOT for patients with COPD, likely owing to the paucity of data available to guide such a practice.

Notably, the costs of LTOT are substantial, as is the burden for patients. Regarding the current literature, unanswered questions at this time include how frequently to monitor patients with mild to moderate COPD to assess for the development of worsening hypoxemia, as well as the possible benefit of LTOT during pulmonary rehabilitation. Patients appear to benefit from pulmonary rehabilitation, and patients with moderate COPD may feel too breathless to exercise without oxygen.¹² Patients with COPD with moderate hypoxemia who have symptoms of breathlessness with rest and exertion may still benefit from LTOT, especially if it increases their exercise tolerance and ability to perform daily activities. Further trials should focus on the subset of patients with COPD who have moderate hypoxemia and dyspnea on exertion. Randomized, blinded studies should monitor the effect of LTOT on the symptoms and exercise capability of this subset of patients.

Conclusion

The dogmatic prescription of LTOT for patients with COPD should be challenged, as the morbidity and mortality benefit of this treatment in patients with COPD with moderate hypoxemia remains unproven. However, data suggest that symptom relief in a subset class of patients with COPD may improve with exercise.¹³ Therefore, pending further data, prescription of LTOT on an individual basis is likely to proceed for now. Further studies may be justified to clarify potential benefits of LTOT in specific patient outcomes, such as breathlessness during exercise. Also, prescription practices should be aligned with a goal of symptomatic relief in patients with severe hypoxemia or mild to moderate hypoxemia with demonstrable symptomatic benefit, especially in the context of pulmonary rehabilitation or an at-home exercise program. (doi:10.7556/jaoa.2018.145)

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