Long-Term Oxygen Therapy

Roberto Walter Dal Negro • Richard Hodder
Editors

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New Insights and Perspectives

Forewords by Marc Miravitlles and Dario Olivieri

Springer

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To Rick, a distinguished scientist full of humanity:
when a good friend of mine disappears, part of my life is missing

Foreword

When cure is not an option, there is no doubt that the main outcome of treatment of a chronic and debilitating disease is to improve survival. This is also true for chronic respiratory diseases, such as – but not limited to – chronic obstructive pulmonary disease (COPD). Despite the recent advances in pharmacotherapy, no new drug, neither bronchodilators nor anti-inflammatory agents, have been shown to prolong survival in COPD; however, since the early 1980s we know that the use of long-term oxygen therapy (LTOT) in patients with COPD and hypoxemia prolongs life in compliant patients.

For the last 30 years, LTOT has been irreplaceable in patients with severe COPD and resting hypoxemia. However, research has continued and other indications of LTOT have emerged. In addition, the criteria and systems of delivery for LTOT have improved and the evaluation of patients both before and during therapy have also been further developed.

It is believed that aspects related to LTOT belong to the respiratory specialist. It is true that most of the research and the management of patients under this therapy is carried out by pulmonologists. Nevertheless, this is an example of a necessary interaction between the pulmonologist, community doctor, respiratory therapist and healthcare institutions to provide an adequate network to help patients under this type of long-term and costly treatment. Last but not least, we cannot forget the expectations and needs of the patients under LTOT. It is crucial to provide the adequate delivery systems to improve compliance and help the patients to preserve their quality of life, which, in many cases, can be severely impaired.

In this context, it has been a pleasure to welcome the initiative of this book entitled *Long-Term Oxygen Therapy. New Insights & Perspectives*, edited by two great and recognized experts, Dr. Dal Negro and Dr. Hodder. This is a very comprehensive and up-to-date book covering all aspects that clinicians, researchers and healthcare professionals need to know about LTOT. The authors are an impressive list of

specialists, mainly Italian but with recognition well beyond their country, and with known expertise in the field. I find the initiative to gather together all aspects related to this form of therapy, starting from the patient candidate for LTOT, to the expected outcomes of treatment, particularly interesting. Moreover, one section of the book is dedicated to a review of the role of all sectors involved in LTOT: the lung physician, general practitioner, caregivers, healthcare institutions and even the role of the media. Of course, a whole section is dedicated to the needs and perspectives of patients.

I want to congratulate Dr. Dal Negro and Dr. Hodder for gathering together this outstanding group of authors and developing this book, which will provide information to all readers interested in the state of the art of LTOT. I am also sure that reading this book will alert readers to some aspects that still need more research and questions that, after 30 years, still remain unanswered. In an era when there is a great proliferation of scientific journals online and information circulates extremely fast on the internet, it is clear that we need references to search for valid knowledge, the knowledge that has been elaborated and filtered by real experts. This is the role of this book, and the interested reader can find in its pages everything that needs to be known about this important therapy for our respiratory patients.

I only wish that future publishers will continue this important contribution to the respiratory field.

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Foreword

Have you ever wondered just how important the *patient's perspective* is to ensure success with long-term oxygen therapy (LTOT)? It is widely known that in chronic diseases, patient compliance is essential for a positive outcome - the treatment will not be effective *if you do not take your medicine*. LTOT, however, is more complex and demanding than just taking a pill. The treatment is day and night and requires the use of sophisticated machinery and cooperation between the patient and his/her healthcare providers. The *patient's perspective* is very important since his/her commitment to the therapeutic regimen needs to be guaranteed in order to reach therapeutic goals.

The work by Roberto Dal Negro and Richard Hodder focuses on the importance of patient well-being and compliance as well as the value of encouraging the patient to actively participate in his/her care to ensure optimal therapeutic outcomes. A potential candidate for LTOT must be identified and involved in the decision-making process. The following multidimensional parameters must be carefully evaluated in the patient: pulmonary, cardio-circulatory, metabolic and neuromuscular. Furthermore, the patient's psychological and cognitive profile must be defined and carefully considered. Recent studies have underscored the diversity in patient perspectives when facing the prospect of LTOT and the discomfort it may incur in their daily life.

The patient must feel appropriately surrounded by competent healthcare providers who are ready to intervene as necessary. The caregivers must all be on the same wavelength. The general practitioner must work in collaboration with the pulmonologist by transferring care of the patient back and forth as necessary. Importantly, healthcare centres need to be available and sensitive to the patient's needs according to the situation at hand. The media can play an important role in sensitising society to the serious problems these patients face and the importance of prompt social and medical intervention.

This brilliant and up-to-date book by Dal Negro and Hodder does not limit itself to citing general principals and guidelines for LTOT, but rather delves deep into the various modes of oxygen administration and the details of managing LTOT treatments. LTOT is a standard outpatient therapy complete with benefits and limitations, but there is also the potential for tele-control of the patient's condition and parameters, thereby facilitating the evaluation of the effects of therapy.

Based on these premises, the outcomes that the authors expect, stated at the end of the technical and methodological chapters, are reasonable. Clinical outcomes based on the patient that can be objectively documented. Outcomes that consider not only respiratory function but also the patient's quality of life, including humanistic aspects. The work concludes with a general vision of the impact of LTOT on the patient's needs.

Anxiety, depression, antisocial behaviour and somatoform conditions are the conditions most commonly reported in patients with chronic obstructive pulmonary disease (COPD) and chronic respiratory insufficiency. Moreover, the discomfort mentioned by patients being treated for COPD with LTOT ranges from dyspnoea and limitations on mobility due to the oxygen device to the *stigma of a poor body image.* Unfortunately, these factors lead many patients to stay home and contribute to self-isolation and subsequent depression.

While several of these aspects may already have begun prior to starting LTOT, they tend to worsen with time and interfere with lifestyle and physical activity. The discouraged patient thereby justifies his/her reluctance to use oxygen and subsequent non-adherence to therapy. This behaviour degenerates with time and in relation to the patient's dependence on treatment. The patient's effort to accept treatment varies over time, generally increasing as the disease progresses. The patient's sense of frustration increases accordingly and he/she realizes that they are increasingly dependent on oxygen therapy in order to feel better.

In conclusion, the complexity of these factors makes the issue of LTOT extremely important and current for both the patient and physician. This work is timely and current considering the periodic updates in the literature on COPD and its treatment with LTOT. A wholehearted thanks to all the authors and editors for their efforts in creating this excellent work.

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The Patient Candidate for Long-Term Oxygen Therapy

1

Roberto W. Dal Negro and Richard Hodder†

1.1 A Brief History of Oxygen Therapy

Very little oxygen existed when our earth was formed approximately 4.6 billion years ago, but atmospheric oxygen gradually increased over time and for the past 100 million years the atmospheric concentration of oxygen has been similar to what we enjoy today. Nowadays, we take oxygen for granted as something that supports day-to-day life and as a life-saving therapy when needed, but the history of clinical oxygen therapy and particularly of long-term oxygen therapy (LTOT) is a relatively recent phenomenon [1-3].

The concept of oxygen as a therapeutic agent evolved from the work by several physiologists of the 17th century. Oxygen was first identified in 1772 in Sweden by Scheele (who called it *fire air*), and was independently isolated from heating mercuric acid by Joseph Priestly in England in 1774. Priestly hinted at possible therapeutic properties of this *dephlogisticated air* when he speculated that: *It might be particularly salutary to the lungs in certain morbid cases when the common air would not be sufficient to carry off the phlogistic putrid effluvium fast enough.* Not long after, Antoine Lavoisier named the gas *oxygen*.

Oxygen was apparently first used as a therapeutic agent by Thomas Beddoes in the early 1800s at his Pneumatic Institute in Bristol, England [4], and until the early 20th century it was popular as potential therapy for a wide range of disorders including cholera, syphilis, hysteria and infertility, occasionally being administered by enema. However, when no consistent positive results were observed, enthusiasm for oxygen therapy diminished, until in the 1920s, when it was recognized that oxygen

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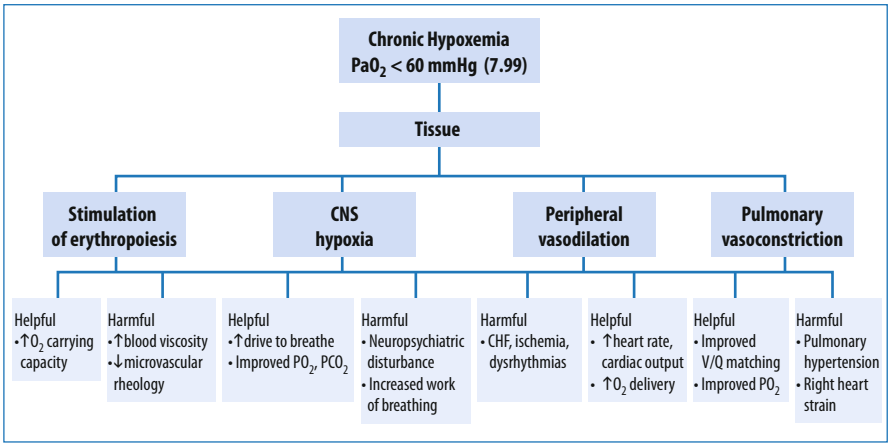

Fig. 1.1 Consequences of chronic hypoxemia

deficiency could result in serious physiological derangements (Fig. 1.1) and that these could be partially reversed by breathing supplemental oxygen. Paralleling these observations, it became possible to commercially produce oxygen using the fractional distillation of liquid air, and to measure the oxygen saturation of blood.

Subsequently, the famous physiologist J. B. S. Haldane used oxygen to treat chlorine gas poisoning during World War I and advocated its use in other respiratory disorders [5]. In Edinburgh, in 1921, the Canadian, Jonathan Meakins, successfully used oxygen therapy to reverse oxygen desaturation in the blood of patients with pneumonia [6]. Following the publication of his observations, oxygen therapy became the standard practice for pneumonia.

In the United States, Alvin Barach first used oxygen to reverse hypoxemia in the 1920s and recognized the potential role of continuous oxygen therapy to treat patients with hypoxemic chronic obstructive pulmonary disease (COPD) [7]. Outpatient use of oxygen was investigated by Cotes in 1956 in the UK [8] and by Barach [9] in the US in 1959. Domiciliary use of oxygen to reduce polycythemia and pulmonary hypertension was studied in detail in the late 1960s, and the potential for increasing longevity with oxygen in COPD was first demonstrated in 1970 by Neff and Petty [10]. The two landmark studies on the role of supplemental oxygen in severely hypoxemic COPD patients, the British Medical Research Council (MRC) [11] and the US National Institutes of Health's nocturnal oxygen therapy trials (NOTT) [12] were published in 1980-1981, and have subsequently formed the basis of current LTOT programs throughout the world. The medical community has subsequently embraced LTOT and it has been estimated that there are likely over a million patients receiving some form of this therapy worldwide [13-14].

1.2 Rationale for LTOT

The consequences of living with chronic hypoxemia can be adaptive, as in healthy individuals living at high altitude [15-16], or harmful, for example in patients with lung disease and other comorbidities (Fig. 1.1) [12, 15-19]. Thus, the rationale for providing chronically hypoxemic patients with LTOT is to slow down, prevent, or reverse those maladaptive consequences that can lead to reduced functioning, health-related quality of life (HRQoL), and longevity. Furthermore, given the widespread biological actions of oxygen, additional benefits of LTOT might exist including: changes in ventilatory control, alterations in pulmonary blood flow, modulations of gene expression and cellular phenotype [16], and modulation of systemic inflammation [19-20] and lung remodelling in response to injury [16, 21-22].

Only a few therapies have been shown to prolong survival in patients with advanced COPD [18, 22], including LTOT [11-12, 23], smoking cessation [24], influenza [25] and pneumococcal [26] vaccination, non-invasive ventilation for acute exacerbations of COPD [27], lung volume reduction surgery in selected patients [28], and possibly sustained bronchodilator therapy [29-31]. Of these interventions, LTOT has the greatest overall impact. The precise reasons for improved longevity with LTOT are unknown and likely multifactorial, as discussed earlier. We know for example, that early LTOT can reduce pulmonary hypertension [11-12, 32-35], and improve exercise capacity [35-42], all of which could contribute in various ways to prolonging life expectancy [18, 32-33, 43]. In addition to hypoxemia, other predictors of survival in COPD patients receiving LTOT include age, disease progression, frequency of COPD exacerbations, COPD phenotype [44], reduction in pulmonary hypertension [35, 45], improvement in maximum oxygen consumption during exercise [35], hypercapnia, anemia [46] and the presence of co-morbid illnesses [11, 23, 47-49]. Traditionally, untreated hypoxemic COPD has been felt to be associated with polycythemia with its attendant potentially harmful consequences of pulmonary hypertension, reduced cerebral blood flow, and increased risk of thromboembolic disease (Fig. 1.1) [19]. However, more recent observations have suggested that polycythemia may be less of a problem than anemia in COPD [46]. In one large series, a hematocrit > 55% was observed in only 8.4% of patients with severe COPD, perhaps because these patients were all on LTOT [46]. Anemia of chronic disease may be prevalent in advanced COPD as a reflection of systemic inflammation [46, 50-51], or as a consequence of occult renal failure and impaired production of erythropoietin that has been observed in elderly patients with COPD [52]. By improving oxygen delivery to all tissues in hypoxemic patients, LTOT has the potential to correct altered hemoglobin levels. Indeed, in a 3-year telemetric study of patients with severe hypoxemic COPD, LTOT use was associated with a normalization of hemoglobin in both polycythemic and anemic patients [50].

From the patient's perspective, it is possible that in addition to improving survival,

Table 1.1 Factors affecting clinical response to LTOT

Pulmonary disease factors
• Severity of hypoxemia
• Chronicity of hypoxemia
• Nature of lung disease (e.g. COPD, pulmonary fibrosis, etc.)
• Presence/absence of pulmonary hypertension
Oxygen therapy factors
• Dose of LTOT
• Adherence to LTOT
• Ambulatory oxygen prescribed and used or not
• Portable oxygen device weight/ease of use
• Side effects of LTOT (e.g. headaches, dry nasal mucosa, uncomfortable cannulas, device noise, self-image, etc.)
• Complications of LTOT (e.g. burns, tripping over oxygen tubing, exaggerated hypercapnia, etc.)
Patient factors
• Co-morbid disease (e.g. heart, arthritis, psychological factors, sleep-related illness, etc.)
• Nutritional status
• Anemia
• Perception of breathlessness
• Role of hypoxemia in causing breathlessness
• Social and living situation
• Availability and strength of caregiver support
• Adherence to regular exercise program
Healthcare delivery factors
• Availability of pulmonary rehabilitation
• Access to respiratory educators
• Availability of collaborative self-management/chronic disease management program

LTOT might be useful in improving other patient-centred outcomes such as exercise capacity, sleep quality, fatigue, rate of COPD exacerbations, and the need for hospitalization. Chronic hypoxemia has a direct negative influence on HRQoL and neuropsychiatric functioning (e.g. cognition, mood, etc.) [17, 53-56], but only a few studies on how LTOT might improve these important outcomes have been done and results are conflicting. In patients with advanced COPD and resting hypoxemia, some studies have detected no benefit from LTOT on HRQoL [57-59], or neuropsychiatric functioning [54, 60-61], while others suggest a positive influence on either HRQoL [54, 62-63], or neuropsychiatric functioning [12,57, 64-67]. A few investigators have looked at the effects of outpatient LTOT on these outcomes in COPD patients with isolated exertion-related hypoxemia, again with some studies showing small improvements in neuropsychiatric functioning or HRQoL [64], whereas others have not [62,68-69].

Not all patients appear to respond well to LTOT. This is not surprising as, in addition to the degree of hypoxemia, it is likely that several interacting variables are involved in influencing the clinical response to LTOT (Table 1.1), both in real life and in clinical trials. It is not clear for example, what levels of chronic, non-life threatening, hypoxemia will provoke significant tissue hypoxia and subsequent organ dys-

function, as this will modulated by other variables such as the presence of co-morbid illness, hemoglobin levels, cardiac output, the health of the microvasculature, adherence with LTOT, adherence with regular exercise, the availability of pulmonary rehabilitation and educational and psychosocial support etc. Indeed, the values of PO_2< 55 mmHg, and PO_2< 59 mmHg with cor pulmonale or polycythemia, that form the basis of most current LTOT guidelines arose not from the results of the NOTT [12] and MRC [11] trials, as these were not dose finding trials, but rather from the reasonable *a priori* assumptions of trial entry criteria made by the investigators. Nevertheless, the longevity data from the NOTT and MRC trials described below suggest that these blood gas criteria do identify a population of COPD patients likely to benefit from LTOT and it would indeed seem prudent to intervene with LTOT for patients with this degree of hypoxemia. Little formal work on predicting specific hemodynamic responses to LTOT has been done, but there is some evidence that in hypoxemic COPD patients, a reduction in pulmonary artery pressure and an improvement in maximum oxygen uptake during exercise testing as predictors of increased longevity with LTOT in these patients [35, 45]. Because such observations are impractical, LTOT indications will remain based on broader clinical outcomes such as longevity and possibly increased exercise capacity. Whether patients with worse or lesser degrees of hypoxemia would benefit from LTOT is an area awaiting future research.

1.3 The Enduring Legacy of the MRC and NOTT Oxygen Trials

All LTOT guidelines have been derived from two relatively small, non-blinded clinical trials conducted over 30 years ago in a highly selected group of significantly hypoxemic patients with severe COPD [11-12]. The MRC trial [11] attempted to answer the question of whether some oxygen therapy was better than no oxygen therapy, and the NOTT trial [12] investigated whether continuous oxygen therapy was better than only nocturnal oxygen therapy. Both trials studied the effect of low flow oxygen in predominantly elderly (NOTT: ~ 65 years old; MRC: ~ 58 years old), mostly male patients with advanced COPD and resting daytime hypoxemia (NOTT: mean PO_2 51 mmHg, PCO_2 43 mmHg, FEV_1 29% predicted; MRC: mean PO_2 50 mmHg, PCO_2 54 mmHg, FEV_1 0.70 L). NOTT studied 203 patients for a mean duration of 19.3 months (investigators stopped the trial at 38 months feeling it unethical to restrict oxygen to nocturnal use only), and the MRC trial reported on 87 patients over a 5-year follow-up. Oxygen dosing was different between the two trials. In the NOTT trial oxygen at 1-4 L/min was taken for ≥ 19 hours per day in the continuous group and for ≤ 13 hours per day in the nocturnal group, whilst the MRC oxygen group used oxygen for 15 hours per day, usually at 2 L/min.

Taken together (Fig. 1.2), the results of these two trials confirmed that low flow

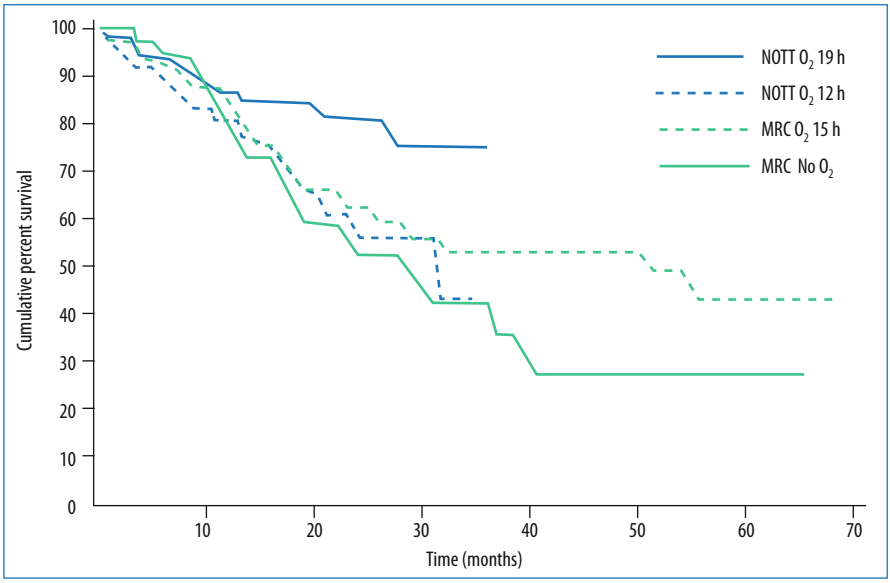

Fig. 1.2 Survival results of MRC and NOTT long-term oxygen trials. Adapted from [63, 157]

supplemental oxygen for > 15 hours per day improves 5-year survival from 25-41% in patients with advanced COPD who have resting daytime hypoxemia defined as a PO_2< 55 mmHg (7.33 kPa), or a PO_2 55-59 mmHg (7.33 - 7.87 kPa) plus evidence of hypoxic organ dysfunction such as cor pulmonale or a hematocrit > 55%. These results have been concisely summarized by DC Flenley [70] in reference to hypoxemic COPD patients as: "*…no oxygen is bad….oxygen for some of the time is better….but oxygen for most of the time is best of all"*. Largely due to ethical considerations, it is difficult to imagine that we will ever repeat placebo-controlled LTOT trials in patients with *significant* hypoxemia (i.e. resting daytime PO_2< 55 mmHg) regardless of the underlying cause of the hypoxemia.

Despite modern management strategies for COPD, it remains a progressive illness and so it is logical to expect that the impact of LTOT will diminish with time in individual patients. Indeed, an uncontrolled 12-year LTOT observational trial in patients similar to those studied in the NOTT and MRC trials demonstrated a 5-year survival of 62% (better than NOTT, MRC), but only a 26% 10-year survival [23].

As noted earlier, while based upon sound reasoning, the fixed limit for a qualifying PO_2< 55 mmHg is somewhat arbitrary, and it is quite possible that some individuals with milder degrees of hypoxemia may benefit from LTOT. A placebo-controlled trial investigating the role of LTOT in COPD patients with milder hypoxemia (resting daytime PO_2 of 56-65 mmHg) has reported that over ≥ 3 years, LTOT did not provide longevity benefits [71-72]. Similarly, a trial of nocturnal LTOT in COPD patients

with mild resting daytime hypoxemia and isolated nocturnal hypoxemia was unable to demonstrate improved longevity, nor did nocturnal oxygen slow down either the progression of pulmonary hypertension, or the time to the onset of significant daytime hypoxemia requiring full LTOT. Although neither of these trials was powered to show a statistical effect of LTOT on survival, taken together they suggest that COPD patients without significant daytime hypoxemia are unlikely to live longer with LTOT, at least based upon group mean data. This hypothesis currently under active investigation (see below).

1.4 Current LTOT Guidelines and Selection of Patients for LTOT

Providing LTOT is an expensive therapy [73-78] with a real potential for abuse by inappropriate prescription [78-85]. Thus, in order to limit its use to those most likely to benefit, most countries offering LTOT follow prescribing guidelines based upon the MRC and NOTT studies [86]. A sample of various guidelines is shown in Table 1.1 and reveals only minor inconsistencies [47, 86-90]. However, some guidelines do suggest a possible role for LTOT in circumstances not currently supported by solid evidence-based data and it is these areas that define the need for further large-scale studies. An algorithm representative of the commonly used approach to screening and prescribing LTOT is shown in Figure 1.3. Many, perhaps the majority, of LTOT prescriptions are initiated when patients are hospitalized for an exacerbation of COPD. Despite the fact that many funding agencies require a reassessment of the patient's

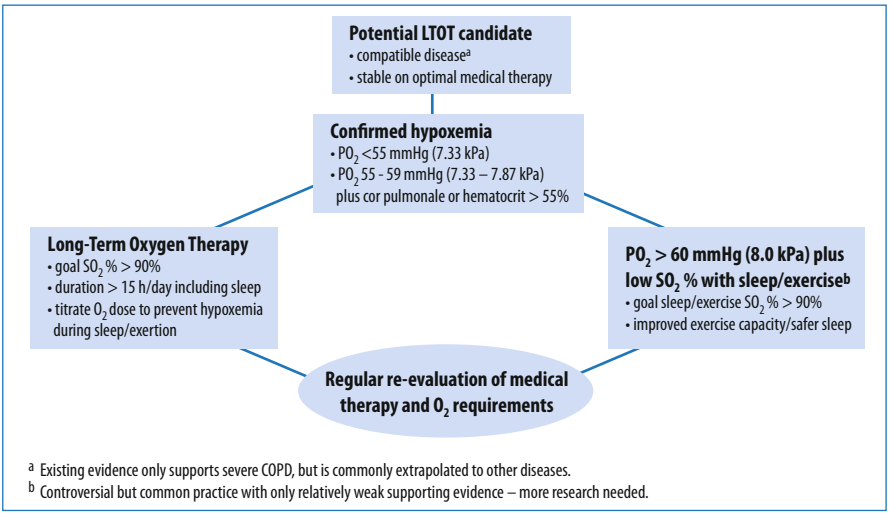

Fig. 1.3 LTOT selection algorithm

Table 1.2 Clinical criteria for selecting potential LTOT candidates

Degree of hypoxemia (FIO2 = 0.21)	GOLD	ATS/ERS	NICE	AIPO
Severe	PaO_2 < 55 mmHg (7.33 kPa) or SpO_2 ≤ 88%	PaO_2 < 55 mmHg (7.33 kPa) or SpO_2 ≤ 88%	PaO_2 < 55 mmHg (7.33 kPa)	PaO_2 < 55 mmHg (7.33 kPa)
Moderate	PaO_2 of 55 to 59 mmHg (7.33-7.87 kPa) or SpO_2 of 89% plus at least one of the following criteria: • pulmonary hypertension • peripheral oedema • hematocrit > 55%	PaO_2 of 55 to 59 mmHg (7.33-7.87 kPa) or SpO_2 of 89% plus at least one of the following criteria: • cor pulmonale • peripheral oedema • hematocrit > 55%	PaO_2 of 55 to 59 mmHg (7.33-7.87 kPa) or SpO_2 of 89% plus at least one of the following criteria: • pulmonary hypertension, • peripheral oedema • secondary polycythemia • *nocturnal desaturation for more than 30% of sleep	PaO_2 of 55 to 60 mmHg (7.33-7.99 kPa) plus at least one of the following criteria: • hematocrit > 55% • signs of pulmonary hypertension • signs of hypoxia (peripheral oedema of right heart failure, mental decline) • *ischemic heart failure
Normoxemia at rest	No recommendation	*PaO_2 ≥ 60 mmHg (7.99 kPa) or SpO_2 >90% plus severe nocturnal desaturation and lung-related dyspnoea responsive to oxygen	No recommendation	*Intermittent oxygen may be indicated for: • desaturation (SpO_2 < 90%) for more than 30% of sleep • in presence of exercise-related desaturation

* not currently evidence-based.
GOLD, Global Initiative for Obstructive Lung Disease; *ATS*, American Thoracic Society; *ERS*, European Respiratory Society; *NICE*, National Institute for Health and Clinical Excellence; *AIPO*, Italian Association of Hospital Pulmonologists.

ongoing need for supplemental oxygen once stable post hospital discharge, some evidence suggests that this is not done in a majority of cases [91-94]. This underlines the important role for collaborative self-management and integrated care which emphasizes good communication and cooperation amongst the various healthcare professionals and agencies involved in providing LTOT in the context of chronic disease management [95-101].

When selecting patients for possible LTOT, clinicians (and patients) need to appreciate that dyspnoea alone is insufficient to justify a prescription for oxygen [102]

Table 1.3 Clinical criteria for selecting patients for LTOT

- Confirmed diagnosis of a disease capable of causing chronic hypoxemia
- Optimized medical therapy
- Disease stability
- Confirmed smoking cessation[a]
- Confirmation that supplemental oxygen reverses hypoxemia[b]
- Confirmation that supplemental oxygen confers clinical benefit if provided for improving exercise capacity[c]

[a] Not mandatory in all jurisdictions; [b] Not always rigorously documented;
[c] Not universally required.

and that certain other clinical criteria should be confirmed (Table 1.2). Even in patients with COPD and significant resting hypoxemia, there is only mixed evidence that supplemental oxygen will relieve breathlessness when such patients are at rest [57-58, 60, 102-105]. There is even less evidence supporting the use of LTOT to treat resting breathlessness in patients without significant resting hypoxemia [102, 106], although one recent systematic review has suggested that LTOT may improve symptoms in this type of patient and that oxygen prescription should be individualized [105]. On the other hand, there is good evidence that oxygen therapy will reduce exertion-related breathlessness in COPD patients with both resting and isolated, exertion-related hypoxemia (see below) [41, 102, 107-109]. In this regard, clinicians should be aware that prescribing LTOT without an outpatient facility can have a tendency to reinforce sedentary lifestyles in patients by forcing them to stay indoors [110, 111].

COPD clinical practice guidelines are somewhat vague in making recommendations regarding continued smoking and the prescription of LTOT [112-113]. Smoking prevalence in patients on LTOT is poorly studied, but is probably in the range of 20-30% and physicians must advise prospective LTOT patients on the safety hazards of this practice [112]. Despite the fact that 38-43% of patients in the original MRC and NOTT LTOT trials continued to smoke [11-12], it is generally believed that continued cigarette smoking may negate the benefits of LTOT in COPD by virtue of increasing carboxyhemoglobin levels and so limiting the desired oxyhemoglobin and hematocrit responses [114], as well as contributing to COPD progression and opening the door for fire-related injuries [115] (Table 1.3).

Despite a lack of firm supporting evidence, these MRC/NOTT inspired LTOT guidelines have been extrapolated for use in hypoxemic patients with diseases other than COPD such as interstitial lung disease [116-118], bronchiectasis [119], cystic fibrosis, kyphoscoliosis [120], chronic congestive heart failure, etc., and this seems reasonable, particularly because it is unlikely that any large scale, placebo-controlled clinical trials of LTOT will ever be conducted in hypoxemic patients from these groups. One recent survey in Italy is representative of the worldwide experience and has documented the relative infrequency of LTOT prescriptions for conditions other than COPD over the past 2 decades (Fig. 1.4) [121].

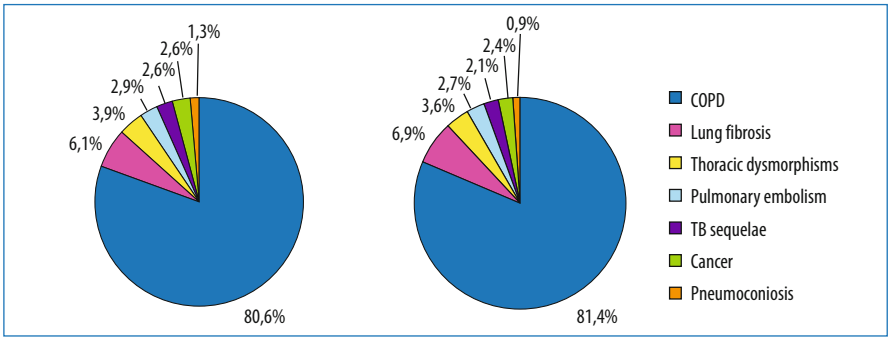

Fig. 1.4 Most common reasons for prescribing LTOT in Italy from 1990-2004 (n= 2204)114 and updated to 2011

1.5 The Patient's Perspective on LTOT

The responses of patients facing the prospect of LTOT are very individualized, as can be seen from the following quotes taken from typical patients using LTOT for advanced COPD [122-125]:

"*For me, emphysema is gasping old men on oxygen. What a way to live!"*
"One of the main reasons I quit smoking is that I didn't want to end up on oxygen."
"*I feel like everybody is staring at me….I just feel like a freak"*
"I think I feel like it's shameful because I have to do it because I smoked"
"If you know it's there, you seem to relax, but if you say to yourself: "I have no oxygen", then you start to panic…"
"You have to use it in moderation. If you're going to use it all the time, you're going to become dependent on it…"
"I thought oxygen would confine me. But I proved it didn't. It freed me. I could golf and travel again!"
"Oxygen is my life support system. Without it, I'd die."
"Oxygen is no big deal. It's like any other piece of clothing that I wear all day, every day. It's become part of my life."

Clearly, many patients appear to be conflicted when LTOT is recommended and acceptance of LTOT should not be taken for granted. Some patients welcome LTOT because they perceive it to be a therapy that will help them live longer and more active lives. Such well-informed patients recognize that LTOT can be liberating by opening up new opportunities for them to increase activities of daily living (ADL), both basic and instrumental. They thus see LTOT as an enabling therapy that will help them

to regain a measure of lost independence and social interaction, and so provide an opportunity to lead more normal lives. Some will experience reduced breathlessness with ADL and exercise and will thus become more motivated to adhere to prescribed exercise training. Even if LTOT is not used as prescribed, many patients are reassured by the fact that it is available if needed (i.e. for breathlessness) [122] and this may help to reduce the likelihood of panic attacks and so improve their quality of life.

Other patients may react negatively to a prescription for LTOT and far from welcoming it as a hopeful new therapy, an oxygen prescription may be seen as a sign of advanced disease and that the end of life is near [123-124, 126-127]. This forced glimpse into their own mortality and the realization that they will forever be tethered to an oxygen source, can have a significant depressing effect on patients that eliminates any optimism that their lives will get better [122, 126, 128]. This may be especially true for patients who feel confined indoors to a stationary oxygen device, so that LTOT can in fact create suffering by forcing them to make compromizes to their lifestyles that represent significant losses of independence, autonomy and self-perception [125-127]. LTOT is also perhaps the most visible of chronic therapies and exposes the patient's illness for all to see. It should therefore not be surprising that some patients, especially those with minimal social support, may react to the disability imposed by advanced COPD and the need for LTOT, by withdrawing from others in an attempt to hide their disability. Such a state of *invisible disability* can threaten their self-esteem when they must invent explanations for their lack of social interaction that do not acknowledge their illness [129]. They may feel ashamed of having to rely upon others and paradoxically, have trouble in gaining recognition because of their self-imposed isolation and concealment of their disease.

Thus patients prescribed LTOT may easily become conflicted by wanting to maintain mastery over their disease and take advantage of the liberating potential of LTOT, but at the price of having to accept dependency on oxygen therapy [122, 126]. This fear of dependency on oxygen may be an explanation for the common observation of poor adherence with LTOT, especially ambulatory oxygen (see below) [59, 125]. Healthcare professionals may play an unwitting role in poor patient adherence to LTOT, if they do not fully appreciate that using LTOT can be a profound challenge for some patients and fail to support and advise them adequately [126]. Indeed, clinicians enthusiastic for the benefits of LTOT often discover that convincing patients that LTOT can be liberating for them is not always a simple matter.

Many of the challenges facing patients starting LTOT can be solved by good communication between healthcare professionals and patients and their caregivers. Sadly, this may not be the reality for most, as patients frequently report that they had only a single brief conversation about LTOT with their physicians at the time of initial prescription [125]. All involved healthcare professionals need to appreciate the challenges faced by patients starting LTOT (which will be highly individualized) and should regularly re-evaluate and reassess the patient's success or concerns with adjusting to