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EXPERT REVIEWS

Outcome measures for palliative oxygen therapy: relevance and practical utility

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Dyspnea is a common symptom in many advanced malignant and non-malignant diseases and often is refractory to the usual therapies. In such circumstances palliative care approaches are necessary and among them palliative care oxygen therapy can be applied although currently its effectiveness is rather uncertain. Palliative oxygen therapy can be given on either continuous basis or on demand. Often the continuous palliative oxygen therapy is seen as long-term oxygen therapy although their aims are rather different. Palliative oxygen therapy was evaluated in populations with mixed underlying diseases, with outcome measures not only the most appropriate for the setting and therefore these limitations might have influenced the overall perceived therapeutic benefit. Therefore an evaluation of this method in subsets defined based on the etiology and pathogenic mechanisms and with appropriate outcome measures would help to better define the criteria for its indication and would increase its acceptability.

KEYWORDS: oxygen therapy • chronic obstructive pulmonary disease • lung cancer • palliative care dyspnea

Home oxygen therapy has been used over the past three decades to correct moderate-to-severe hypoxemia in patients with chronic respiratory failure in order to increase their survival and to palliate symptoms such as dyspnea in patients with oncological malignancies and limited survival period. In both settings, oxygen can be given continuously or non-continuously, depending on the requirement.

The most commonly used regimen of home oxygen therapy is also known as long-term oxygen therapy (LTOT) and is the approach for which the most standardized recommendations exist (**Box 1**). They are based on the results of two large-scale studies, the Medical Research Council (MRC) Study and the Nocturnal Oxygen Therapy Trial (NOTT), and are valid worldwide [1].

Palliative oxygen therapy is a therapeutic method with narrower applicability and acceptability, is more popular in countries such as Australia, the UK and the USA and has become better known as such during the past several years as a result of the overall expansion of the palliative care approaches [2,3]. This method targets dyspnea that is refractory to the usual therapies, but its effectiveness is still questionable and seems to be case-sensitive. These limitations might be also due to the fact that the existing studies enrolled mostly patients with various underlying diseases, the samples studied were not always large enough and the outcome measures for effectiveness were not always selected in a proper manner. The lack of appropriate outcome measures and that of target populations are probably among the major reasons for the modest efficacy of this therapy, and therefore, these two issues should be reconsidered in order to develop appropriate indication criteria. This review discusses the potential outcome measures in palliative oxygen therapy comparing them with those used in home oxygen therapy. The literature search was performed by accessing the Medline database for both home oxygen therapy and palliative oxygen therapy.

Survival

Generally, it is considered that a palliative care approach is only able to improve the quality of life if the patient is not at the end-of-life stage or it is aimed at increasing its personal comfort during the mentioned stage.

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Box 1. Indications of long-term oxygen therapy.

- Chronic severe hypoxemia paO2 ≤55 mmHg or ≤7.3 kPa, or SaO2 ≤88% ± hypercapnia.
- Chronic moderate hypoxemia paO2 56–59 mmHg (7.3–8 kPa) and signs of pulmonary hypertension, congestive heart failure or polycythemia (hematocrit >55%).

Data taken from [1].

However, in the case of palliative oxygen therapy the question if this therapy is able to increase survival is absolutely appropriate especially if this is prescribed for patients with various organ diseases, including malignancies and persistent severe hypoxemia; however, such data do not exist probably also because only the alleviating role of palliative care oxygen therapy was usually considered as the main therapeutic benefit of this method and other effects on outcome measures such as survival were ignored.

Indeed the oxygen therapy regimen, that is, if domiciliary or on demand should be taken into consideration.

The current guidelines recommend domiciliary oxygen therapy as a palliative care approach in patients with lung cancer and an estimated survival period of no more than 6 months, irrespective of the existence or of the absence of hypoxemia [4,5]. The data on the effectiveness of such approach are very limited, and in particular, the potential benefit of domiciliary oxygen therapy on survival is actually unknown. Because of this knowledge gap, it is also difficult to predict which of these patients might actually benefit the most in terms of survival from such a method. If an extrapolation from chronic respiratory failure due to chronic obstructive pulmonary disease (COPD) is done, then it can be expected that individuals with severe hypoxemia or with moderate hypoxemia and signs of right heart disease due to persistent hypoxemia might have an increased survival.

In fact, there are several seminal studies performed in patients with COPD and severe hypoxemia ($PaO_2 \leq 55$ mmHg) and in whom various regimens of domiciliary oxygen therapy were evaluated for their effects on survival. The MRC was a British controlled study that evaluated over a period of 3 years the effects of a 15 h (including sleep hours) oxygen therapy regimen in patients with advanced COPD and hypoxemia in whom it was found to improve significantly the chances of survival, especially in the longerterm [6].

The NOTT was an American study that evaluated comparatively the effects of nocturnal versus continuous oxygen therapy (COT) in patients with COPD and found that the former oxygen therapy regimen was associated with a significant better survival than the nocturnal method especially in patients with a more impaired lung function, psychological status and poor exercise capacity [7].

In both studies, the survival benefit became significant after more than 12 months, that is, after more than 500 days in the MRC study and after 24 months in the NOTT study. These effects can be correlated with the disease trajectory and with slower decline in the case of chronic respiratory failure due to nonmalignant pulmonary conditions. In patients with malignancies, given the steeper allure of the disease trajectory and consequently the shorter survival, it is difficult to believe that home oxygen therapy would be able to prolong to such a comparable extent the survival, but this discordance should not prevent us from studying the effects of COT in such a population. However, methodologically such a study is rather difficult because of the need for a control group. The use of historical controls is appropriate, provided both treated and untreated populations have as common denominator the comparable levels of hypoxemia.

Palliative oxygen therapy on demand is usually considered for severe refractory dyspnea and the existing evidence is rather against this therapeutic method [8].

However, most often, in these studies patients with oncological conditions were included, the main measures of effectiveness were usually represented by the impact on symptom (e.g., dyspnea) severity, the short-term effectiveness was usually evaluated and the impact on survival was not considered as an immediate and appropriate outcome of benefit.

Health-related quality of life

As mentioned before, quality-of-life improvement represents the essence of palliative care, and based on this assumption, it is expected that such a beneficial effect might also be exerted by oxygen therapy.

Health-related quality of life (HRQL), measured using disease-specific questionnaires, is an important clinical outcome for patients with severe COPD. Quality of life is impaired even in patients with milder COPD, including those with minimal breathlessness while performing strenuous exercise. In these severe cases, HRQL may represent a more relevant outcome than survival [9]. In such patients, LTOT is expected to improve the HRQoL by reducing dyspnea, anxiety and depression, and by enhancing emotional function and mastery, but for some, LTOT is unacceptably limiting and intolerable [10].

The studies performed on domiciliary oxygen therapy that is used to correct hypoxemia in advanced COPD showed discordant results based on the fact that the duration was variable, mostly the sample sizes were very small and different quality-of-life tools were used. In the NOTT, the largest sample of patients was included and the HRQL was assessed using a generic questionnaire, the sickness impact profile [7]. However, an analysis of the effect of oxygen therapy on its scores was never published independently from the master paper discussing the overall results. The other subsequent studies used a disease-specific questionnaire, the Saint George Respiratory Questionnaire (SGRQ), and evaluated the short-term effects on domiciliary oxygen therapy initiation. Some of these studies reported a significant improvement in SGRQ scores in treated patients compared to placebo on a short-term basis, whereas others failed to detect such an effect on a long-term basis [10,11].

Another study using the SF-36 and SGRQ noted worse scores in a low-income COPD population that used oxygen therapy [12]. A randomized study failed to find an advantage in HRQoL of ambulatory oxygen over placebo in COPD patients who did not meet the criteria for mortality reduction with

LTOT, thus not supporting the general 'off-label' application of this treatment in patients not meeting the recognized criteria for LTOT [13].

The effects of ambulatory oxygen on HRQoL were assessed in patients with exertional dyspnea and COPD, and the results were contradicting and probably tool-sensitive because those using the SGRQ reported improvements in HRQoL [10,14,15].

In a study performed to assess the effects of a 7-day course of palliative oxygen therapy in patients with various advanced non-malignant diseases or cancer, the quality of life was evaluated using a generic questionnaire, the McGill Quality of Life Questionnaire, which failed to show any significant improvement in its scores in patients with oxygen therapy as compared to those on room air [16].

In the setting of palliative oxygen therapy, the quality-of-life evaluation raises some methodological aspects; these are mainly related to the choice of the tool(s), which is crucial for the practical relevance of such an assessment. If the relief of the dyspnea is firstly considered, then a disease-specific questionnaire should be used. In the case of diseases such as COPD, congestive heart failure or lung cancer, the oxygen therapy is the most commonly prescribed therapy. However, apart from dyspnea, other symptoms such as fatigue and other components of the quality of life such as psychological or social domains are important for patients who are prescribed for palliative oxygen therapy. If these aspects are to be considered, they are best assessed by a generic questionnaire, that is, a tool that can be applied irrespective of the underlying pathology. A combined generic and disease-specific questionnaire could be feasible to evaluate most if not all possible aspects of the quality of life.

However, the amount of data supporting the beneficial effects of palliative oxygen therapy on HRQoL is very low, probably because most of the prospective studies evaluating the outcomes of palliative oxygen therapy focused mainly on dyspnea burden and only marginally assessed the quality of life.

Respiratory symptom burden: palliative oxygen therapy & refractory dyspnea

The hospice movement has become increasingly involved in the management of life-threatening, both malignant and non-malignant diseases, which is currently approached in a multidisciplinary manner. Dyspnea is the final, tragic symptom of COPD and many other respiratory diseases but can become severe and distressing even before the end-of-life stage and can represent a therapeutic challenge. Dyspnea is one of the most distressing symptoms experienced by patients. It is a combination of a 'sensation' (neural activation resulting from stimulation of a receptor) and a 'perception' (reaction of the individual to that sensation) [17]. Dyspnea refractory to the usual therapy represents an indication for palliative care that should be provided either in the pulmonary disease unit or in the palliative care unit. Currently, the majority of the patients are more likely to be treated for this symptom in the former than in the latter units. The main aims of palliative care oxygen therapy are to reduce the severity of respiratory symptoms and especially that of dyspnea and to improve the functional status [8]. However, the overall effects of this therapeutic method in relieving dyspnea are rather modest and surpassed by those of opioids and benzodiazepines [18]. This might be explained by the fact that the recommendations do not take into account the degree of hypoxemia in indicating the necessity for palliative oxygen therapy.

The precursor of palliative oxygen therapy, the short-term domiciliary oxygen therapy or the non-COT (NCOT), was defined as a daily regimen of less than 12–15 h administered regularly or on an intermittent basis and was designed to reduce dyspnea and to improve the quality of sleep in patients with COPD or with chronic heart failure.

The previous studies evaluating NCOT effects in smaller samples demonstrated a minimal effect of the nocturnal regimen and a clear beneficial effect only in the case of hypoxemia-related dyspnea in COPD [7,19–22].

The most supportive data subsequently came from a study performed within the Danish Registry evaluating the effects of NCOT on breathlessness, well-being, sleep quality and quality of life in 174 patients, 82 receiving regular nocturnal oxygen therapy and 92 receiving it on demand. The overall mean age of the patients was 68.9 years, 25.4% were hypoxemic, the average time spent on oxygen was 5.1 and the diseases for which the oxygen therapy was recommended were COPD (51.1%), cancer (23.4%), cardiac disease (9.9%) or neuromuscular disorders (5%). Dyspnea was evaluated using a 0–10 visual analogue scale (VAS). The most beneficial effects of NCOT were detected on dyspnea and quality of life. The proportion of patients with dyspnea VAS score of at least 5 was 89% before the start of oxygen therapy, and this decreased to 50% under oxygen. The proportion of patients with a dyspnea reduction of at least the minimal clinically important difference (0.5 units of score) was 76.3%. In 43.2% of patients, dyspnea improvement was associated with a similar effect on physical activity. The largest therapeutic effect was detected in patients who were ex- or non-smokers and who had a more severe dyspnea at baseline [23].

It is currently accepted that the NCOT can be given during rest or during exercise. The latter is called ambulatory oxygen therapy and was found to decrease dyspnea severity in patients with exertional mild hypoxemia [10,14].

Palliative oxygen therapy is aimed (at least in theory) at reducing dyspnea irrespective of if it is related or not related to the physical activity, and therefore, both continuous and non-continuous regimens can be used for symptom alleviation.

However, little is known which of these regimens is appropriate for which dyspnea characteristics. The severity of this symptom was actually considered to be the main reason for prescribing palliative oxygen therapy in a study performed in Australia and including 5203 patients, finding that oxygen therapy was more likely to be prescribed for patients with more severe dyspnea with a VAS score of 7.6 (on oxygen) than for those with a VAS score of 4.2 (without oxygen) ($p < 0.01$) [24].

In a prospective 4-year cohort study performed in Australia, palliative home oxygen therapy was prescribed in about 21.1%

(n = 1239) of a population of 5862 patients covered by a community palliative care service. The impact of oxygen therapy on dyspnea was assessed via a VAS (ranging from 0 to 10) at baseline (before oxygen initiation) and 1 or 2 weeks afterward in 413 subjects, and it was found that the mean baseline dyspnea score was 5.3 and that the home oxygen therapy had no significant impact on dyspnea severity irrespective of the underlying disease or demographic factors. Particularly in patients with oncological conditions receiving home oxygen therapy, it was found that this therapeutic method had no significant impact. Therapy responders were patients who at 1 or at 2 weeks exhibited a dyspnea improvement of at least 20%, and 115 fell in this category [25].

However, in this study, the analysis was not performed according to the hypoxemia degree, the type of oxygen regimen used was not clearly mentioned (i.e., continuous or burst) and the scale used was only a quantitative visual scale and not a dyspnea questionnaire.

In a most recent study 239 patients with refractory dyspnea caused by various diseases such as COPD, lung cancer and other respiratory or cardiac diseases were enrolled and were randomized to receive oxygen therapy (120) or to breath room air (119), and dyspnea was assessed using two different scales and with a diary covering various symptom dimensions and quality of life was also evaluated. Oxygen therapy failed to improve dyspnea significantly compared to the room air irrespective of the time of the day when it was measured (morning, evening) and the largest effect was detected in patients with moderate-to-severe symptoms [16].

The above-mentioned studies all included a mixed population of patients with both oncological and non-oncological conditions, and their results were rather concordant and not supporting the use of palliative oxygen therapy as a therapy for refractory dyspnea.

However, it should be taken into account that the severity (and the complexity) of the symptom is also driven by the underlying pathogenic mechanisms and that the most severe dyspnea is always diagnosed in patients with chronic progressive respiratory diseases. This is supported by the results of a study demonstrating that in patients with advanced COPD and hypercapnic failure, the dyspnea severity and mood disturbances were worse than in patients with lung cancer [26,27].

Therefore, the picture might look different if seen from different angles. If COPD is taken into consideration, the existing data might be in favor of the effectiveness of palliative oxygen therapy even in patients with mild or no hypoxemia and who consequently do not qualify for domiciliary oxygen therapy. In fact, a meta-analysis performed on 18 trials that included 702 patients reported that oxygen therapy was able to significantly reduce the dyspnea level [8]. Such results support the use of palliative oxygen therapy beyond the current indications of home oxygen therapy, but still further studies should be carried out in order to support this approach.

The same reasoning might also apply for patients with dyspnea due to end-stage heart diseases; however, in this population, there were only few studies evaluated the effectiveness of palliative home oxygen therapy and therefore more studies should be carried out to obtain conclusive and reliable results [28].

In patients with oncological conditions and mainly with lung cancer dyspnea irrespective if transient or persistent can occur in 20–70% of them [26]. However, the more episodic character of dyspnea, the higher the likelihood of normoxemia and the more common association of dyspnea with pain might make the oxygen therapy for palliative purposes to be less appropriate.

In fact, in patients (n = 134) with cancer who were normoxemic or with mild hypoxemia while experiencing dyspnea refractory to other therapies, palliative oxygen was not able to improve significantly the symptom severity [29].

Therefore, the role of oxygen in the management of dyspnea in non-hypoxemic oncological patients is questionable despite its wide clinical use.

In such patients, opioids should be used as the first-line therapy, whereas in patients with dyspnea and hypoxemia, the initial use of oxygen seems to be more plausible [30–32].

Effort tolerance & functional status

Ambulatory oxygen was evaluated for its ability to improve not only dyspnea and quality of life but also for its effects on effort tolerance and functional status [15,33]. If the functional status was not directly measured in such studies, effort tolerance measured with the distance walked was evaluated. The resulting data failed to demonstrate a certain beneficial effect on exercise capacity probably because of the different designs, variable study periods and small samples enrolled [10,13,14,34,35]. Similar results were obtained in a more recent randomized study that enrolled 144 patients with both normoxemia or hypoxemia during exertional dyspnea, and in whom oxygen was administered during physical effort for 12 weeks [15].

Emotional distress & cognitive impairment

People with severe progressive disorders are often subjected to a high risk of psychological distress that has a complex etiology. The most commonly encountered disorders are represented by anxiety and depression; their prevalence increases toward the end-of-life stage, and their management usually requires a multidisciplinary approach involving physicians, social workers and spiritual assistants [36,37]. In the case of patients with COPD, for example, the prevalence of anxiety is three times higher than that in the normal population and depression is also commonly encountered, and both have a negative impact on quality of life and disease-related morbidity [38,39].

In patients with hypoxemic COPD, such symptoms are directly related to the underlying hypoxemia and it is expected that domiciliary oxygen therapy is able to reduce their severity in an indirect manner. However, the data on this specific disease population are scarce: for example, in the NOTT study, the neuropsychological status was evaluated in both nocturnal and continuous oxygen arms (n = 150 patients in total), and it was found that at 6 months, it improved the mood status in a

comparable manner in both study subsets. At 1 year follow-up, patients who underwent COT had significantly improved mood status as compared to patients under nocturnal oxygen therapy [40].

In a subsequent study performed only in 10 patients, the therapeutic effects of home oxygen therapy were apparent although there was no statistical significance after the first 3 months [41].

Cognitive impairment was detected in patients with COPD and is considered to be related to hypoxemia, and home oxygen therapy was reported to reduce the risk of its development [42].

In the case of palliative oxygen therapy, however, it is not known whether the therapy can improve the mood status significantly. Therefore this aspect should be further evaluated and in case of a demonstrated therapeutic benefit, this should be used as an argument for a wider use in palliative care setting.

Caregiver burden

The additional burden of palliative oxygen in patients with refractory dyspnea is not known. This burden might related to the oxygen therapy device used and to the effort required from the caregivers to supervise its correct administration.

In a study evaluating in both patients and nurses the perception of home oxygen therapy reported that factors of favorable perception of this method were represented by the detectable therapeutic benefit, familiarity with the device and compliance maintenance [43].

Furthermore, the caregivers might be facilitators toward initiation of domiciliary palliative oxygen therapy; in a prospective study performed in the patients with refractory dyspnea at end-of-life stage and in whom palliative oxygen therapy was prescribed, it was found that this method was significantly less likely to be prescribed in patients who lived alone (11.8 vs 20.6%; $p < 0.001$), in those having oncological diseases (18.8 vs 26.5%; $p < 0.001$) and in older people (68.1 vs 69.6 year; $p = 0.005$). The lack of a caregiver was also associated with a significantly higher medical burden in patients with severe dyspnea (VAS score of at least 7/10) who required twice as many physician visits before oxygen initiation (4.2 vs 1.7; $p = 0.03$) [24].

However, the effectiveness of LTOT in palliating dyspnea as perceived by the caregivers still remains uncertain like the dimensions and severity of their burden related to this therapeutic method [44].

Expert review & five-year view

Palliative oxygen therapy still remains an underprescribed and underused therapeutic method and this limitation has several consequences.

First, all the definition of palliative oxygen therapy is not very clear and it varies worldwide. In the current understanding of the meaning and as discussed in this review, a palliative therapeutic method should be aimed at alleviating symptom or symptoms and quality of life without being able to prolong survival.

In this setting, the symptom should be represented by dyspnea refractory to other therapies and hence it is expected that oxygen therapy should reduce its severity. However, the available studies failed to demonstrate any significant benefit, and this might be due to the small size of the samples used and the fact that a sensitivity analysis in patients according to hypoxemia levels was never considered.

Another gap in the current knowledge on the effects of palliative oxygen therapy on dyspnea is the fact that in the existing studies all evolutive types of dyspnea, that is, episodic and continuous were assessed together.

The etiology of dyspnea in the studied patients might also influence the effectiveness of this method and this should also be considered in the future studies.

Most of the existing studies used as a dyspnea rating tool, a VAS alone. This is very good at quantifying the perceived severity of dyspnea but is not able to detect the corresponding clinical and functional manifestations of this level of severity. Scales able to fulfill this desiderate can be 'borrowed' from the field of pulmonary disease and can be represented by a symptom scale such as MRC-modified dyspnea scale or dyspnea-12 or can be represented by disease-specific/symptom-specific quality-of-life questionnaire such as SGRQ or chronic respiratory disease questionnaire, the latter including a dyspnea-specific domain.

The evaluation of dyspnea using a quality-of-life questionnaire would have three advantages: first, it would allow to see the impairments discussed above, which correspond to the level of dyspnea severity, and second it would help to see if this method is really able to improve the quality of life, and last but not the least, in the case of such an effect, it would be possible to find out if the patient perceives this improvement by comparing this with the minimal clinically important difference of score.

Another important issue is to differentiate (when appropriate) between long-term domiciliary oxygen therapy and palliative care COT. The former is usually used in chronic respiratory failure with severe hypoxemia to improve survival (and this effect was most substantially demonstrated in patients with underlying COPD), whereas the latter is usually indicated in patients with a limited predicted survival (usually less than 6 months) and its effect on survival is actually not known and at least not considered when recommending it.

The palliative role of oxygen in episodic dyspnea should also be further clarified especially in patients with concomitant (transient) hypoxemia. In the setting of respiratory diseases, such patients usually do not qualify for continuous domiciliary oxygen therapy but can benefit from using home oxygen therapy as ambulatory oxygen therapy (for exertional hypoxemic dyspnea) or as short-burst oxygen therapy (for episodic resting hypoxemic dyspnea).

Further studies are needed in order to better define the indications and the target populations for palliative oxygen therapy, and in doing this endeavor, the use of appropriate outcome measures would be of tremendous help.

Such studies would also allow to better delineate the palliative/symptomatic oxygen therapy from corrective ('functional') oxygen therapy or on the contrary would help in finding their common denominator(s).

To conclude, despite current limited or modest effectiveness, palliative oxygen therapy remains an important therapeutic method and its importance as well as its therapeutic (re)positioning can be better documented after identifying the appropriate measures of effectiveness.

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Key issues

- Oxygen therapy is usually prescribed for patients with chronic respiratory failure as home oxygen therapy in order to improve their survival and is most commonly administered continuously (at least 15/24 h).
- Palliative oxygen therapy is mainly aimed at treating refractory dyspnea in patients with both malignant and non-malignant conditions and is an underused method of therapy.
- It can be prescribed as both continuous or on demand.
- The effectiveness of palliative oxygen therapy is uncertain, and this can be due to the fact that the target populations that would benefit the most are not well defined, and because the outcome measures of effectiveness are not well standardized.
- If measures such as survival, quality of life, mood status, dyspnea or functional status would be evaluated, the benefits of palliative oxygen therapy would be better known and exploited.

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