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Randomised trial of ambulatory oxygen in oxygen-dependent COPD

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ABSTRACT: Long-term oxygen therapy may limit a patient's ability to remain active and may be detrimental to the rehabilitation process. This study aimed to determine the effect of ambulatory oxygen on quality of life and exercise capacity in patients with chronic obstructive pulmonary disease fulfilling the usual criteria of long-term oxygen therapy.

In a 1-yr, randomised, three-period, crossover trial, 24 patients (mean age 68 yrs; mean arterial partial pressure of oxygen at rest 7.1 kPa (53 mmHg)) were allocated to one of the six possible sequences generated by three interventions: 1) standard therapy (home oxygen therapy with an oxygen concentrator only); 2) standard therapy plus as-needed ambulatory oxygen; and 3) standard therapy plus ambulatory compressed air. The comparison of ambulatory oxygen *versus* ambulatory compressed air was double blind. The main outcomes were quality of life (Chronic Respiratory Questionnaire), exercise tolerance (6-min walk test) and daily duration of exposure to oxygen therapy.

The trial was stopped prematurely after an interim analysis. On average, the patients used few ambulatory cylinders (7.5 oxygen cylinders *versus* 7.4 compressed air cylinders over a 3-month study period). Ambulatory oxygen had no effect on any of the outcomes.

In conclusion, the current results do not support the widespread provision of ambulatory oxygen to patients with oxygen-dependent chronic obstructive pulmonary disease.

KEYWORDS: Chronic obstructive pulmonary disease, exercise, oxygen therapy, quality of life, randomised controlled trial

Long-term oxygen therapy (LTOT) is the only component of the management of chronic obstructive pulmonary disease (COPD) that is known to improve survival [1, 2]. Other aspects of the treatment of COPD are primarily aimed at the alleviation of symptoms [3]. In Canada, LTOT is usually provided by stationary oxygen concentrators and is recommended to be used for $\geqslant$15–18 h·day^{-1}. Such a therapeutic regimen limits the ability of the patients to remain active and may be detrimental to the rehabilitation process. The use of ambulatory oxygen in conjunction with domiciliary oxygen has been proposed as a solution to this problem [4–6].

The use of ambulatory oxygen could also increase compliance with LTOT [7], a potentially important effect given the dose-dependent effect of oxygen on survival. In addition, the correction of exercise-induced oxygen desaturation may increase exercise tolerance and, therefore, help to maintain patients' autonomy [8]. The current study was designed as a randomised, double-blind, crossover trial to test the hypothesis that, in patients on LTOT, ambulatory oxygen (in addition to the use of a home oxygen concentrator) would improve health-related quality of life (QoL) and exercise capacity when compared with the use of a home oxygen concentrator alone. In addition, it was hypothesised that ambulatory oxygen added to the use of a home oxygen concentrator would improve overall compliance with LTOT.

METHODS

Setting

The trial took place between November 1999 and October 2003 in three respiratory homecare programmes in the province of Quebec, Canada. These programmes were funded by the Quebec universal medical insurance plan, which delivers homecare (mainly LTOT and related services) to registered patients with any chronic lung disease. During the study period, no ambulatory oxygen was supplied out of protocol, even to those who were not eligible or refused to participate.

Study eligibility

Outpatients with COPD diagnosed by a history of past or current smoking and obstructive

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disease were eligible. Only patients meeting the following criteria for LTOT were included: arterial partial pressure of oxygen (P_{a,O_2}) $\leqslant$7.3 kPa (55 mmHg); oxygen saturation $\leqslant$88%; or P_{a,O_2} $\leqslant$7.8 kPa (59 mmHg) with clinical evidence of at least one out of pulmonary hypertension, right ventricular hypertrophy, cor pulmonale or haematocrit $\geqslant$55% [2]. The patients had been on LTOT for $\geqslant$3 months (to avoid the inclusion of patients who were prescribed oxygen following an acute exacerbation of COPD and who may not have fulfilled LTOT criteria upon re-evaluation), but for no longer than 12 months. Clinical stability was demonstrated by no exacerbation or change in medication for $\geqslant$6 weeks before enrolment. The ability to give informed consent was mandatory. The following patients were excluded: 1) those who already owned portable oxygen cylinders; 2) those who had been hospitalised more than three times in the previous year for respiratory failure; 3) those who were currently participating in a respiratory rehabilitation programme; or 4) those who had end-stage COPD. The latter were housebound and had, in the current authors' opinion, no potential for rehabilitation or had a vital prognosis <18 months. The eligible patients were systematically identified from the records of the three homecare programmes and were invited to participate in the trial.

Interventions

This trial compared the use of home-based oxygen therapy alone (delivered through stationary oxygen concentrator) with ambulatory oxygen added to home-based oxygen therapy. Home oxygen was delivered to achieve a P_{a,O_2} >8 kPa (60 mmHg) [1]. Ambulatory oxygen was delivered through small pressurised cylinders (PulseDose EX-2000D; DeVilbiss, Sunrise Medical, CA, USA; fig. 1) [9]. As some of the benefits obtained from ambulatory oxygen therapy can be ascribed to a placebo effect [10], a third study period was included, where patients were provided with portable compressed air. The pressurised cylinders containing compressed air had the same external appearance as those containing oxygen, allowing the comparison of ambulatory oxygen *versus* ambulatory compressed air to be double blind.

During a 1-month run-in period, clinical stability of those who accepted to participate was ascertained. New prescriptions of either a long-acting bronchodilator or theophylline were not allowed beyond the run-in period. Oxygen titration was performed during this period to maintain a saturation of $\geqslant$90% during ambulation. The patients were also familiarised with the ambulatory gas delivery system and instructed to use it when going out, in order to preserve normal oxygen saturation during ambulation and to extend the duration of exposure to oxygen. Following the run-in period, those who fulfilled the criteria were submitted to three consecutive interventions: 1) standard therapy (home oxygen therapy with an oxygen concentrator only); 2) standard therapy plus as-needed ambulatory oxygen; and 3) standard therapy plus as-needed ambulatory compressed air. The three 3-month treatment periods (one for each intervention) were separated by 1-month washout periods. Therefore, the total duration of the trial was 1 yr. The distribution of the cylinders was managed by the respiratory staff working for the homecare programme. The patients were instructed to pick up the cylinders at their respective study site. Due to strict federal regulations regarding gas transportation, three cylinders were provided at a time, with no restriction on the total amount of cylinders that the patients could use. In case of acute exacerbation, evaluation and treatment were left to the treating physician. No restriction was made on the treatment regimen used during the exacerbation.

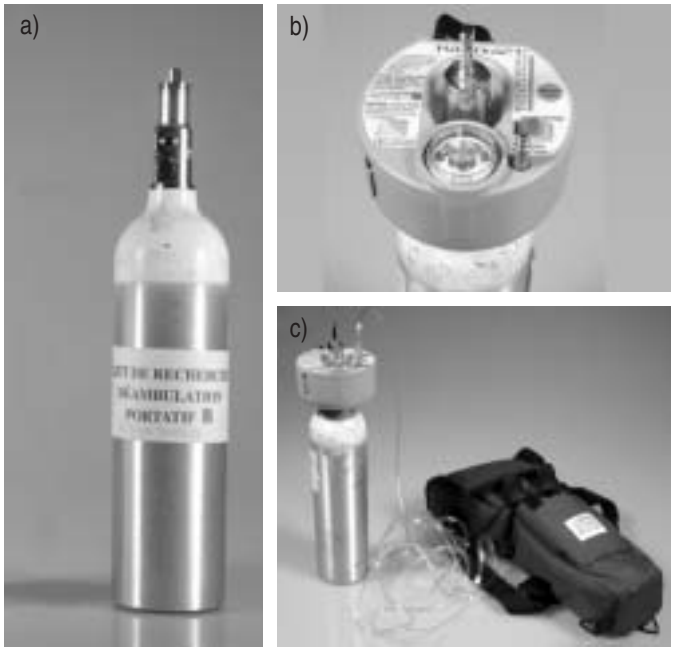

FIGURE 1. The ambulatory oxygen system included a) a small pressurised 2.5-kg cylinder, 35 cm in height, containing 160–180 L of oxygen coupled with b) an oxygen-conserving device that delivered pulses of oxygen only during early inspiration, therefore extending the duration of oxygen supply. The cylinders containing compressed air had the same external appearance as those containing oxygen. c) The whole system weighed 3.5 kg and was carried by the patients themselves.

Randomisation and blinding

The patients were randomly allocated, in blocks of six, by using sealed envelopes, to one of the six possible sequences generated by the three interventions. The sequences were concealed until the interventions were assigned. The randomisation process was the responsibility of a research nurse not otherwise involved in the trial. The outcomes were assessed by a research assistant unaware of the treatment sequence.

Outcomes

The primary outcome of the trial was disease-specific QoL. Exercise tolerance represented a secondary outcome. Compliance to home oxygen therapy and ambulatory cylinder utilisation were monitored throughout the study. The Chronic Respiratory Questionnaire (CRQ) was selected as the primary measure instrument [11]. The CRQ is a disease-specific instrument that measures dyspnoea, fatigue, emotional function and mastery (the extent to which patients feel they can cope with the disease and its manifestations). All four domains have performed well in detecting small treatment effects [12]. A difference in score of 0.5 corresponds to the smallest difference in score that patients view as important and that would mandate a change in their management [13]. In

addition, at baseline, the Medical Outcome Survey-Short Form 36 was administered [14]. For comparison, data obtained from a Canadian age-matched population was used [15]. Exercise tolerance was assessed using 6-min walking tests (6MWT) that were performed according to standard methods [16]. The patients carried the cylinders themselves during the tests. A change of >55 m is usually considered as the minimal clinically important difference (MCID) [17]. The daily duration of oxygen use through the stationary concentrator during each treatment period was measured using the concentrator's counter clock. The daily duration of oxygen (or compressed air) use through the portable system was measured by recording the number of cylinders used by the patients. Patients were also asked to self-report their use of the stationary and portable systems by completing a daily diary card.

Statistical analysis

The concordance between the oxygen utilisation from the concentrator's counter clock and the self-reported number of hours of concentrator utilisation was evaluated using the intra-class correlation coefficient (ICC) [18]. The same statistic was helpful in determining the concordance between the utilisation of compressed air cylinders and that of oxygen cylinders. Analyses of variance were used to compare the treatment effects computed from the difference in scores under each study condition [19]. Prior to testing the treatment effect, two additional factors were incorporated into the regression model. Both the effect of time (*i.e.* whether a change has occurred between the study periods) and the sequence effect (*i.e.* whether the order in which the treatments were given produced a difference that could not be explained by the specific action of the individual treatments) were examined. The present trial also tested for the carry-over effect (*i.e.* the effect that occurs when the effect of a treatment extends beyond its period of application to influence the action of a subsequent treatment) [20]. The mean treatment effects were all adjusted for the measure obtained at the beginning of the period. Similar analyses of variance were used to compare the number of hours of oxygen and cylinder utilisation throughout the trial. Finally, the dose-response relationship between the number of oxygen cylinders used and the change in outcome during the corresponding period was examined using regression analyses.

It was determined that 43 patients were needed to give a 90% chance of showing a statistically significant difference in CRQ scores between two study periods, with a two-sided significance level of 5%, if the true benefit of portable oxygen reached the MCID (0.5 per item) [12]. An interim analysis was scheduled for when half of the needed sample size had completed the study. Stopping rules were stated *a priori*. The trial could be stopped if the treatment effect reached significance at the 0.001 level [21] or if the 95% confidence intervals around the primary outcome excluded the MCID. All analyses were run blind.

RESULTS

Flow of participants and follow-up

In total, 668 patients were screened and the trial profile is depicted in figure 2. The reasons for the exclusion of 496 subjects are also detailed in figure 2. The 40 patients who were randomised were those felt to be the most likely to benefit from ambulatory oxygen. Thirteen patients withdrew after randomisation, three died (two from respiratory failure and one from laryngeal cancer undetected at study entry) and 10 could not be submitted to the outcome assessment in due time because of an acute exacerbation of COPD. Table 1 summarises the baseline characteristics of the 24 patients who had completed the trial at the time of the interim analysis. Table 2 presents the results of the QoL assessment at baseline.

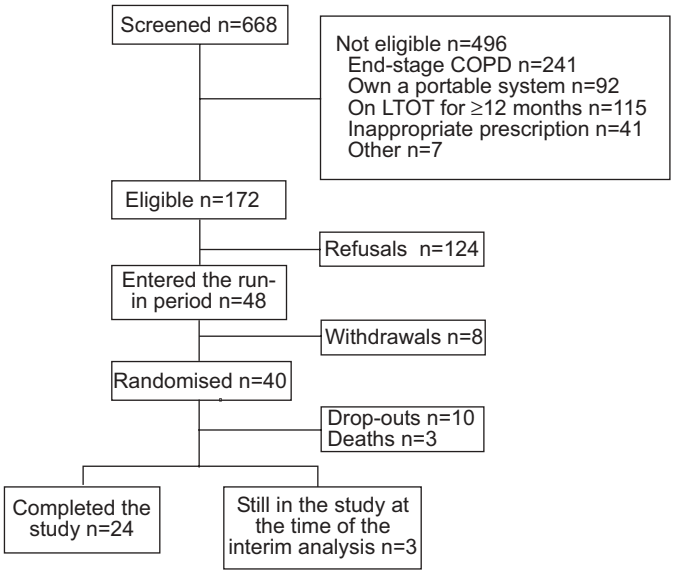

FIGURE 2. Trial profile. COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy.

Oxygen utilisation

The objective measure of home oxygen utilisation from the concentrator's counter clock correlated with the self-reported concentrator utilisation (ICC 0.68; $p<0.001$). Whatever the study period, the patients spent ~18 h·day^{-1} on their

TABLE 1 Baseline characteristics of participating patients

Subjects n	24
Males/females n	11/13
Age yrs	68±8
Time since introduction of LTOT weeks	15±11
Current smokers n (%)	7 (29)
FEV_1 % pred	38±16
$D_{L,CO}$ % pred	38±16
P_{O_2} at rest mmHg room air	53±4
P_{CO_2} at rest mmHg room air	50±7
6MWD with ambulatory oxygen m	235±65
6MWD % pred#	50±15

Data are presented as mean±SD, unless otherwise stated. LTOT: long-term oxygen therapy; FEV_1: forced expiratory volume in one second; % pred: % predicted; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung; P_{O_2}: partial pressure of oxygen; P_{CO_2}: partial pressure of carbon dioxide; 6MWD: 6-min walk distance. #: reference values from [22]. 1 mmHg=0.133 kPa.

TABLE 2 Baseline generic and disease-specific quality of life scores

	Clinical score	Normative data#
SF-36		
Physical functioning	24±17	76±22
Role emotional	71±46	83±33
Mental health	71±18	79±15
Vitality	51±20	68±18
General health perception	41±18	74±18
CRQ		
Dyspnoea	3.3±0.7	
Fatigue	4.1±1.2	
Emotional function	4.6±0.8	
Mastery	5.4±0.9	

Data are presented as mean±SD. SF-36: Short Form 36; CRQ: Chronic Respiratory Questionnaire. #: age-standardised scores [15].

concentrator (table 3). Few cylinders were used (7.5 oxygen cylinders·patient^{-1} (range 0–46) *versus* 7.4 compressed air cylinders·patient^{-1} (0–42) over a 3-month study period; p=1.0). None of the participants reported any adverse events related to the handling or transportation of the cylinders. A significant correlation was found between the utilisation of compressed air cylinders and that of oxygen cylinders (ICC 0.60; p<0.001). On average, the patients went out of their home for 2 h·day^{-1}. Despite the unrestricted provision of cylinders, the patients went out three times more often without cylinders than with the oxygen or air cylinders. The added exposure to oxygen from the portable cylinders was limited to an average of 30 min·day^{-1}.

Treatment analysis

No placebo effect of ambulatory compressed air or any real treatment effect of ambulatory oxygen was observed on any of the four domains of the CRQ. All changes in QoL scores were close to zero and surrounded by narrow confidence intervals excluding the MCID (fig. 3; table 4). Based on this finding, the decision was made to stop the trial after the interim analysis. Similarly, no placebo effect of ambulatory compressed air or any real treatment effect of ambulatory oxygen was observed on the 6MWT. All differences were close to zero and surrounded by narrow confidence intervals excluding the MCID.

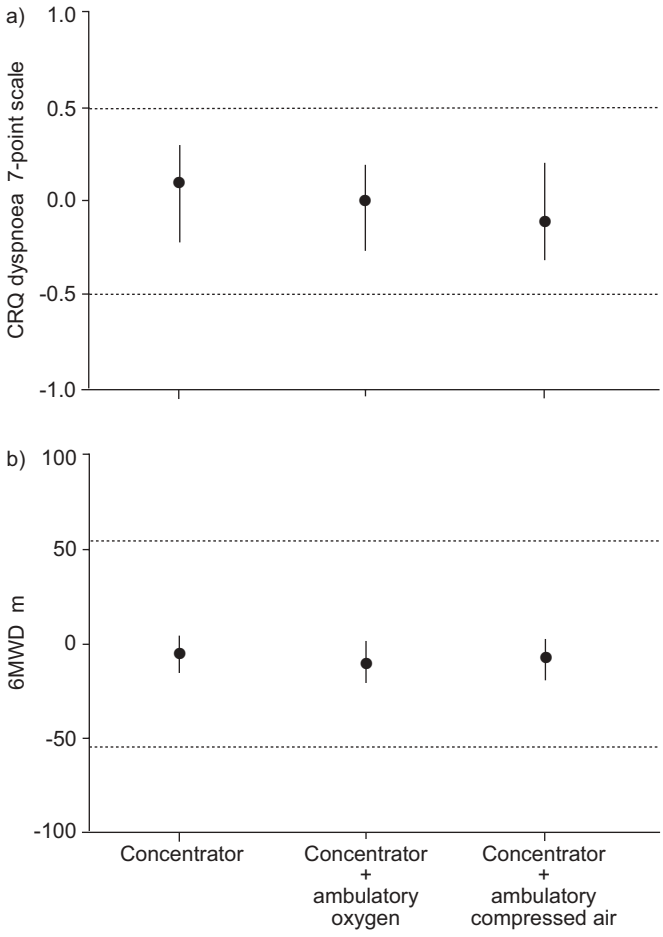

FIGURE 3. Changes in a) Chronic Respiratory Questionnaire (CRQ) dyspnoea scores and b) 6-min walked distance (6MWD) compared to the minimally clinically important differences (·····; 0.5 and 55 m, respectively) in the three study periods.

Time, sequence and carry-over analyses

A statistically significant time effect for all the outcomes was observed. The changes between the study periods occurred randomly, could not be explained by the natural course of the

TABLE 3 Number of hours per day of exposure to oxygen

Outcome	Concentrator alone	Concentrator + ambulatory oxygen	Concentrator + ambulatory compressed air	p-value#
Oxygen concentrator use				
From counter clock reading	18.0 (17.2–18.7)	17.4 (16.7–18.0)	18.0 (17.3–18.7)	0.32
Self-reported	18.3 (17.5–19.0)	18.4 (17.5–19.2)	18.4 (17.6–19.3)	0.95
Time spent out of the home				
Without using ambulatory cylinders	1.7 (1.2–2.1)	1.3 (0.8–1.8)	1.4 (0.9–1.8)	0.46
Using ambulatory cylinders		0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.99¶

Data are presented as mean (95% confidence interval), unless otherwise stated. #: p-value from the analysis of variance comparing the treatment effects obtained under the three study conditions; ¶: comparison of oxygen concentrator + ambulatory oxygen *versus* oxygen concentrator + ambulatory compressed air only.

TABLE 4 Quality of life and functional exercise capacity

Outcome	Concentrator alone	Concentrator + ambulatory oxygen	Concentrator + ambulatory compressed air	p-value#
CRQ				
Dyspnoea¶	0.1 (-0.2–0.3)	0.0 (-0.3–0.2)	-0.1 (-0.3–0.2)	0.67
Fatigue¶	0.0 (-0.2–0.3)	0.1 (-0.1–0.4)	0.2 (-0.1–0.4)	0.72
Emotional function¶	-0.1 (-0.3–0.2)	-0.2 (-0.5–0.1)	-0.1 (-0.2–0.1)	0.71
Mastery¶	-0.1 (-0.4–0.2)	-0.1 (-0.3–0.2)	0.0 (-0.2–0.3)	0.77
6MWT+	-5 (-15–5)	-11 (-21–1)	-7 (-17–3)	0.72

Data are presented as mean (95% confidence interval), unless otherwise stated. CRQ: Chronic Respiratory Questionnaire; 6MWT: 6-min walk test. #: p-value from the analysis of variance comparing the treatment effects obtained under the three study conditions; ¶: score per item (7-point scale); +: metres.

disease and were smaller than the MCID. No significant sequence or carry-over effects were found.

Dose-response analysis

No correlation could be found between the use of ambulatory oxygen (expressed in terms of number of cylinders used during the study period) and changes in any of the outcomes during the corresponding period.

DISCUSSION

The results of the present trial challenge the recommendation that active patients receiving LTOT should have both stationary and mobile systems of oxygen delivery [4–6]. In this study, individuals were carefully selected and were considered to be the most likely to benefit from ambulatory oxygen. According to the current criteria, only a minority of patients with oxygen-dependent COPD would be eligible for ambulatory oxygen (fig. 2). This situation should have favoured the finding of positive results. In this highly selected population and despite unrestricted access to portable oxygen, the study patients used very little ambulatory oxygen. Moreover, the patients went out three times more often without cylinders than with cylinders. Ambulatory oxygen had no effect on any of the outcomes in the intervention. Although the sample size was small, the width of the observed confidence intervals demonstrated that the negative results were not from a lack of power to detect a clinically significant difference (fig. 3). Therefore, the negative results were interpreted as an indication of no benefit from ambulatory oxygen.

Two additional observations suggest that results presented here stem from a ''failure of the intervention'' rather than a ''failure to intervene''. First, the significant correlation between the utilisation of compressed air cylinders and that of oxygen cylinders is an indication that, on average, patients did not perceive any difference between the two interventions. Secondly, there was no ''dose-response effect'' of ambulatory oxygen, as no benefit of ambulatory oxygen could be demonstrated, even among those who used a large number of cylinders.

In total, 92 patients were excluded from the trial because they already owned an ambulatory oxygen system (fig. 2). Most had obtained it from their personal insurance plan. Others (n=22) obtained it before the beginning of the trial from the participating respiratory homecare programme that provided, on a compassionate basis, ambulatory oxygen systems to those who asked for it. There was no difference in age, time since the introduction of LTOT, smoking status, pulmonary function tests and arterial blood gases between the 92 excluded patients and the 24 who participated in the trial. In addition, during the first 12 months of utilisation, the 22 patients who obtained their system from the participating respiratory homecare programme used, on average, over a 3-month period, a number of cylinders not statistically different from what was found in the present trial (data not shown). Therefore, there is no reason to believe that the patients who were excluded from the trial because they already owned an ambulatory oxygen system made more efficient use of their own system than those who participated in the trial.

By virtue of the crossover design, survival could not represent an outcome in this trial. Given that the added exposure to oxygen from the portable cylinders was limited to 30 min·day^{-1}, the effect of portable oxygen on patients' survival is probably not significant. In the British Medical Council's trial, 500 days elapsed before any effect of continuous oxygen therapy appeared, when compared with no oxygen therapy at all [1]. The present authors believe that the effect on survival of portable oxygen in addition to home-based oxygen therapy is very unlikely.

As benefits obtained from ambulatory oxygen therapy are likely to be prone to a placebo effect, a study period where patients were provided with portable compressed air, hence allowing the comparison of ambulatory oxygen *versus* ambulatory compressed air to be double blind, was included. This contrasts with the randomised trials that have looked at the effect of portable oxygen added to home oxygen concentrator in patients with oxygen-dependent COPD [7, 23]. In the 1-yr, open, parallel-group trial, QoL was not formally assessed, and the daily duration of exposure to oxygen was significantly longer in those who had portable systems (17 h *versus* 14 h). It is plausible that this difference was actually related to the absence of double masking [24].

Although a number of short-term studies have demonstrated physiological effects of ambulatory oxygen in patients with COPD [25], the results from the present study are in agreement with other randomised trials of ambulatory oxygen conducted in non-oxygen-dependent COPD subjects. In a 12-week,

randomised, double-blind, crossover trial, McDONALD *et al*. [26] found no impact of exertional oxygen in 26 patients with mild hypoxaemia. Of note, exertional desaturation was not mandatory in this trial. In a similar trial including 41 dyspnoeic, but not chronically hypoxaemic, COPD patients with exertional desaturation $\leqslant$88%, EATON *et al*. [27] found statistically significant improvements in QoL measured by the CRQ. However, for all four domains of the questionnaire, the mean differences between oxygen and compressed air were small and did not reach the MCID.

Who are the patients with oxygen-dependent COPD who could really benefit from portable oxygen? Acute response to ambulatory oxygen does not predict long-term improvement in QoL in patients with COPD not fulfilling criteria for LTOT but with exertional desaturation [27]. Thus, laboratory assessment prior to the prescription of portable oxygen seems inappropriate. Others have suggested that a 3-month period under strict supervision would allow the evaluation of portable oxygen therapy use and the advantage of its maintenance [7]. N-of-1 trials (*i.e.* trials conducted by systematically varying the management of a patient's illness during a series of treatment periods [28]) may represent an opportunity to decide which patients will be provided with ambulatory oxygen on the basis of evidence. Poor acceptability and tolerability are often cited as barriers to ambulatory oxygen [27]. Accordingly, it would be of interest to evaluate whether pulmonary rehabilitation in conjunction with ambulatory oxygen could facilitate compliance. Finally, liquid oxygen could be a more efficient way to deliver oxygen in the context of ambulation [29]. In a randomised trial comparing LTOT provided by a concentrator with small oxygen cylinders for ambulation with liquid oxygen treatment, ANDERSSON *et al*. [30] found that liquid oxygen had a better impact on QoL than concentrator treatment, although liquid oxygen was more expensive.

Conclusion

From a social perspective, the results of the present trial do not justify the widespread provision of ambulatory oxygen to oxygen-dependent chronic obstructive pulmonary disease patients. Factors predicting a positive response to ambulatory oxygen are yet to be identified. Whether a more appropriate and efficient use of ambulatory oxygen may be obtained following a successful course of respiratory rehabilitation also remains to be determined.

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