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Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial

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Summary

Background In fibrotic interstitial lung diseases, exertional breathlessness is strongly linked to health-related quality of life (HRQOL). Breathlessness is often associated with oxygen desaturation, but few data about the use of ambulatory oxygen in patients with fibrotic interstitial lung disease are available. We aimed to assess the effects of ambulatory oxygen on HRQOL in patients with interstitial lung disease with isolated exertional hypoxia.

Methods AmbOx was a prospective, open-label, mixed-method, crossover randomised controlled clinical trial done at three centres for interstitial lung disease in the UK. Eligible patients were aged 18 years or older, had fibrotic interstitial lung disease, were not hypoxic at rest but had a fall in transcutaneous arterial oxygen saturation to 88% or less on a screening visit 6-min walk test (6MWT), and had self-reported stable respiratory symptoms in the previous 2 weeks. Participants were randomly assigned (1:1) to either oxygen treatment or no oxygen treatment for 2 weeks, followed by crossover for another 2 weeks. Randomisation was by a computer-generated sequence of treatments randomly permuted in blocks of constant size (fixed size of ten). The primary outcome, which was assessed by intention to treat, was the change in total score on the King's Brief Interstitial Lung Disease questionnaire (K-BILD) after 2 weeks on oxygen compared with 2 weeks of no treatment. General linear models with treatment sequence as a fixed effect were used for analysis. Patient views were explored through semi-structured topic-guided interviews in a subgroup of participants. This study was registered with ClinicalTrials.gov, number NCT02286063, and is closed to new participants with all follow-up completed.

Findings Between Sept 10, 2014, and Oct 5, 2016, 84 patients were randomly assigned, 41 randomised to ambulatory oxygen first and 43 to no oxygen. 76 participants completed the trial. Compared with no oxygen, ambulatory oxygen was associated with significant improvements in total K-BILD scores (mean 55·5 [SD 13·8] on oxygen *vs* 51·8 [13·6] on no oxygen, mean difference adjusted for order of treatment 3·7 [95% CI 1·8 to 5·6]; p<0·0001), and scores in breathlessness and activity (mean difference 8·6 [95% CI 4·7 to 12·5]; p<0·0001) and chest symptoms (7·6 [1·9 to 13·2]; p=0·009) subdomains. However, the effect on the psychological subdomain was not significant (2·4 [–0·6 to 5·5]; p=0·12). The most common adverse events were upper respiratory tract infections (three in the oxygen group and one in the no-treatment group). Five serious adverse events, including two deaths (one in each group) occurred, but none were considered to be related to treatment.

Interpretation Ambulatory oxygen seemed to be associated with improved HRQOL in patients with interstitial lung disease with isolated exertional hypoxia and could be an effective intervention in this patient group, who have few therapeutic options. However, further studies are needed to confirm this finding.

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Introduction

Fibrotic interstitial lung diseases are associated with substantially reduced health-related quality of life (HRQOL) and survival. In idiopathic pulmonary fibrosis (IPF), the most common and deadly of the idiopathic interstitial pneumonias,[1] antifibrotic therapy lessens decline in lung function but does not improve HRQOL.[2,3] As pulmonary fibrosis advances, exertional breathlessness is triggered by simple activities of daily life. Breathlessness is the strongest determinant of HRQOL in patients with fibrotic interstitial lung disease,[4,5] and can be difficult to manage, both for patients and for their informal carers.

Oxygen desaturation contributes to exercise intolerance in patients with interstitial lung disease. However, few data exist for supplemental ambulatory oxygen use in this group, with most studies done in patients

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See Online for appendix

Research in context

Evidence before this study

The 2011 idiopathic pulmonary fibrosis guidelines did not provide guidance on the use of supplemental oxygen in patients with isolated exertional hypoxia, and although the 2015 British Thoracic Society guidelines state that ambulatory oxygen should not be routinely offered to patients who are not hypoxic at rest, no specific reference to patients with interstitial lung disease was made (except to mention the possible benefit of ambulatory oxygen for individual patients with severe exertional breathlessness). We searched PubMed with the terms "ambulatory oxygen", "supplemental oxygen", "portable oxygen", "exercise/exertion", and "interstitial lung disease" for systematic reviews and randomised controlled trials published up to March 1, 2018, with no language restrictions. Neither a 2016 Cochrane review nor a systematic review published in early 2017 had shown evidence of a consistent effect of supplemental oxygen during short bursts of exercise on dyspnoea. However, many of the reviewed studies were deemed low quality because they were retrospective or uncontrolled, or included only small numbers of patients. Two controlled studies published subsequently showed significant benefits of high-flow oxygen compared with placebo air on endurance time and breathlessness during a cycle ergometer test in the laboratory setting. However, the acute effects of high-flow supplemental oxygen on exercise in a laboratory setting might not translate to benefits of ambulatory oxygen in day-to-day life. We identified no studies of the effect of ambulatory oxygen on quality of life in patients with interstitial lung disease.

Added value of this study

Our findings suggests that, compared with no treatment, ambulatory oxygen improves day-to-day health-related quality of life (HRQOL) in patients with isolated exertional hypoxia. Although further studies are needed to confirm this finding, as the first prospective assessment of ambulatory oxygen in the daily lives of patients with interstitial lung diseases, this study represents a crucial stepping stone towards the delineation of guidelines specific to interstitial lung disease.

Implications of all the available evidence

To our knowledge, the AmbOx study is the first prospective randomised controlled trial of the effect of ambulatory oxygen on HRQOL in patients with interstitial lung disease. The results of this trial, if supported by further studies, will enable delineation of specific guidelines for ambulatory oxygen use in interstitial lung disease. However, further larger studies are required to confirm this finding, to enable further understanding of the predictors of long-term uptake of ambulatory oxygen, and to assess whether long-term ambulatory oxygen use is associated with improvements in survival.

with chronic obstructive pulmonary disease (COPD). Although improved survival was noted in patients with COPD and resting hypoxaemia who used supplemental oxygen for at least 15 h per day compared with patients who used nocturnal supplemental oxygen only,[6] ambulatory oxygen had no effect on mortality or HRQOL in patients with COPD and isolated exertional desaturation.[7] However, interstitial lung diseases are characterised by more frequent and severe exercise-induced desaturation than is COPD,[8] suggesting that studies specifically of interstitial lung disease are needed.[5] The paucity of data for ambulatory oxygen in interstitial lung diseases means that there is no guidance on use of the treatment in national and international guidelines.[1,9,10]

Both a systematic review[11] and a Cochrane review[12] of studies specifically assessing use of supplemental oxygen during exercise tests in patients with interstitial lung disease were inconclusive, although two studies[13,14] published subsequently showed significant benefits of high-flow oxygen compared with placebo air in terms of performance and breathlessness during cycle endurance testing in the laboratory. However, immediate benefits in the test setting do not necessarily translate into improvements in day-to-day HRQOL. Drawbacks of ambulatory oxygen include the weight of the portable oxygen equipment, logistic difficulties of replenishment, travel limitations, and the psychological and social burden of the intervention on patients and their caregivers.[15,16] The effects of high-flow oxygen, used in a pulmonary rehabilitation setting, on exercise performance and breathlessness are under investigation.[17] We investigated whether portable ambulatory oxygen was associated with improved HRQOL compared with no intervention in patients with fibrotic interstitial lung disease.

Methods

Study design and participants

AmbOx was a prospective, open-label, mixed-method, crossover randomised controlled trial done at three interstitial lung disease centres (Royal Brompton Hospital, Aintree University Hospital, and North Bristol NHS Trust) in the UK. Eligible patients were aged 18 years or older, had fibrotic interstitial lung disease, were not hypoxic at rest (transcutaneous arterial oxygen saturation ≥94% on room air) but had a fall in transcutaneous arterial oxygen saturation to 88% or less on a screening visit 6-min walk test (6MWT), and had self-reported stable respiratory symptoms in the previous 2 weeks. Patients were excluded if expected to change treatment during the study. Full inclusion and exclusion criteria are in the appendix (p 1). Approval of the final clinical protocol[18] was provided by the NRES Committee London (Fulham) independent ethics committee (14/LO/0258). All patients provided written informed consent.

Randomisation and masking

Participants were enrolled by clinical research staff. There were two separate randomisation processes.

Participants were randomly assigned (1:1) to order of treatment during the 6MWT (ie, placebo air *vs* oxygen cylinders) and, separately, with an independent randomisation list, to order of treatment during the actual trial period (ambulatory oxygen *vs* no intervention).

Both randomisation lists were generated by the trial statistician at the Royal Brompton Hospital via a computer-generated sequence (the *ralloc* command in Stata version 12). The sequence was randomly permuted in blocks of constant size (ten) to ensure that within each block the sequence of treatment was balanced. The constant block size was chosen because the trial was small. The result was a 2×2 crossover design: a two-sequence, two-period, two-treatment crossover design, with sequences AB and BA. The sequences were established a priori and the program generated the sequences in a random order.

The trial statistician sent the randomisation lists to the Imperial College Clinical Trials Unit (ICTU). ICTU set up and operated an interactive web-based randomisation system (InForm) to administer the randomisation process. To conceal allocation, treatment names were not included in the lists, which were held securely and at a separate site by ICTU, whose staff were completely independent of the trial. ICTU staff assigned participants to the trial groups (ie, the sequence of treatment), and neither the clinical research staff enrolling participants, nor the participants themselves, were made aware of the sequence. The statistician who generated the random isation list was involved in data analysis with an independent statistician, neither of whom knew how ICTU labelled treatments A and B. We did not formally assess the success of masking.

Patients were masked to the content of the cylinders used during the 6MWT (all labelling was covered with concealing black tape). Although assessors gathering data were not masked to treatment assignment, patients completed all study questionnaires without input from the clinical trial researchers. All data were entered by trained clinical trial research staff into an electronic database specifically developed by ICTU, using InForm. Data entry for the primary and key secondary outcomes was done independently at Royal Brompton Hospital by an assessor masked to any information pertaining to the trial, including treatment.

Procedures

At the screening visit (figure 1), patients underwent a 6MWT. If oxygen saturation fell to 88% or less on the first test on room air, a second test was done with a portable oxygen cylinder, with a mandatory 30-min rest after the first test. The flow rate of oxygen was up-titrated to either maintain oxygen saturation greater than 90% for more than half of the test or to a maximum flow rate of 6 L/min.[19] Participants completed 6MWTs in a quiet, 30-m corridor, and were provided with standardised instructions and encouragement according to European Respiratory Society–American Thoracic Society standards.[20]

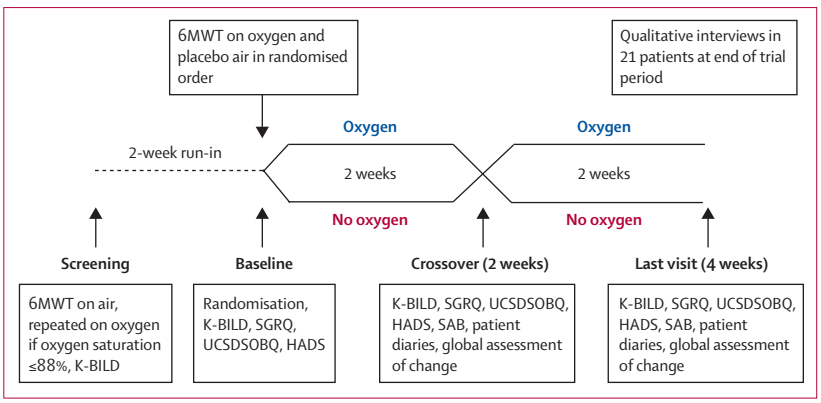

Figure 1: **Trial flow diagram**
6MWT=6-min walk test. K-BILD=King's Brief Interstitial Lung Disease questionnaire. SGRQ=St George's Respiratory Questionnaire. UCSDSOBQ=University of California, San Diego Shortness of Breath Questionnaire. HADS=Hospital Anxiety and Depression Scale. SAB=SenseWear Pro Armband.

At the baseline visit (2 weeks after the screening visit), demographic characteristics including age, sex, smoking history, ethnicity, medical history, and medications were collected. In all patients, diagnosis of type of fibrotic interstitial lung disease was reached by a multidisciplinary team discussion, which was standard protocol at the treatment centres. Pulmonary function tests, including forced vital capacity, FEV_1, and diffusing capacity of the lung for carbon monoxide, and an echocardiogram were done within 6 weeks of the screening visit. If pulmonary function tests or an echocardiogram had been done in the preceding 6 months, they did not have to be repeated. The composite physiological index (CPI) was used as a functional index of lung fibrosis severity at baseline, as previously described.[21] Serum brain natriuretic peptide (BNP) concentrations were measured within 1 month of the screening visit and centrally analysed.

At the baseline visit, patients reporting stable symptoms in the previous 2 weeks (ie, the run in-period), completed two further 6MWTs, one on oxygen and one on placebo air, in random order and at the flow rates identified during the screening visit (continuous flow via nasal cannulae). A rest of at least 30 min between tests was mandatory. 6-min walk distance, oxygen saturation, and heart rate were measured continuously with the WristOx2 3150 (Nonin Medical, Plymouth, MN, USA), and Borg dyspnoea and fatigue scores were measured before and immediately after the test.[22] Time to recovery or return to baseline measurements of heart rate, oxygen saturation, and Borg dyspnoea and fatigue scores were also measured.

After the baseline 6MWTs, patients received either ambulatory oxygen or no treatment for 2 weeks, and then crossed over and received the other treatment for 2 weeks (figure 1). Lightweight oxygen gas cylinders provided ambulatory oxygen. Participants were instructed to use the cylinders during routine activities of daily living. The

cylinders were provided by the relevant oxygen companies (appendix p 1) in the UK according to participants' post code. Cylinder weight was similar for all companies (range 1·8–2·2 kg; appendix p 1). Continuous oxygen flow via nasal cannulae was the standardised mode of delivery. The flow rate established at the screening 6MWT was used. Patients were asked to report, in a dedicated trial paper diary, the number of fully and partially used oxygen cylinders at the end of each week (appendix p 2). Oxygen companies and clinicians completing domiciliary visits were also asked to record oxygen use by participants.

At baseline, week 2, and week 4, patients underwent a physical examination and adverse event assessment, were questioned about concomitant medication, and completed various questionnaires. At the 2-week and 4-week visits, participants' global assessments of change in breathlessness and walking ability were recorded (appendix p 3).

To assess whether ambulatory oxygen was associated with increased physical activity levels in daily life, patients were asked to wear a SenseWear Pro Armband (a biaxial accelerometer; Bodymedia, Pittsburgh, PA, USA) over the body of the triceps for 24 h per day (excluding time for personal hygiene requirements) for 5 consecutive days in each 2-week period. Valid activity was taken as 3 consecutive days with a wear time of more than 89% per day (appendix p 3).

To record participants' experiences of using ambulatory oxygen at home, including benefits and concerns, audio-recorded semi-structured interviews following a topic guide were done by a qualitatively trained research nurse (AF) within 2 weeks of trial completion at the Royal Brompton Hospital only (appendix p 4). Audio-recordings were transcribed, anonymised, and entered into NVivo qualitative data analysis software (version 10) and analysed according to the framework approach—a systematic, well recognised method for qualitative analysis that is based on a process of summarisation and subsequent mapping onto framework matrices, which enables generation of themes.[23] Analysis and interpretation were done by an analytic team (SF, AF, MF, EAR), with the credibility of interpretation reviewed by a patient panel.

Outcomes

Our primary outcome was the difference after each 2-week treatment period between the oxygen and no-oxygen groups in HRQOL, which was measured with the validated King's Brief Interstitial Lung Disease Questionnaire (K-BILD).[24] The K-BILD comprises 15 questions, each with a seven-point response scale, that are grouped into three domains: breathlessness and activities, chest symptoms, and psychological symptoms. The individual domain and total scores can range from 0 to 100, with lower scores indicating worse quality of life.

Key secondary outcomes to measure the effect of ambulatory oxygen on breathlessness during activities were patient-reported global assessment of change (ie, same, better, or worse) in the previous 2 weeks in breathlessness on exertion and ability to walk, and scores on the University of California, San Diego Shortness of Breath Questionnaire (UCSDSOBQ),[25] a well established tool for assessment of dyspnoea during activities. In the UCSDSOBQ, the severity of dyspnoea in 24 activities is ranked on a scale of 0 to 5; the total score can thus range from 0 to 120, with higher scores indicating worse dyspnoea.

To further assess the effect of ambulatory oxygen on HRQOL, other secondary outcomes included scores on the St George's Respiratory Questionnaire (SGRQ) and the Hospital Anxiety and Depression Scale (HADS). The SGRQ is a 50-item questionnaire that was developed for use in COPD but is widely used in IPF.[26] It is divided into three components (symptoms, activity, and impact), with a total score ranging from 0 to 100 (higher scores indicate worse HRQOL). The HADS consists of 14 items, seven for depression and seven for anxiety, with scores on each subscale ranging from 0 to 21.[27] A score of 8 or more on either subscale indicated the presence of anxiety or depression, as appropriate.[28,29] Other secondary outcomes were activity parameter scores for physical activity recorded by SenseWear armbands, oxygen saturation and heart rate over a 48 h period recorded by home pulse oximetry, patient diaries of daily activities, and patient-reported and oxygen company-reported oxygen cylinder use. Data for 48 h oxygen saturation and heart rate and patient diaries are not reported here, but we plan to report them in a later publication. The determinants of the decision to continue on ambulatory oxygen at the end of the trial were also investigated, including demographic variables, smoking history, lung function parameters, and primary and major secondary outcome variables.

Statistical analysis

A sample size of 80 was calculated to be sufficient to detect a significant difference in K-BILD scores between the two study groups. The power calculations were based on a minimal clinically important difference of 8, which was reported in a cohort of 57 patients with interstitial lung disease of widely varying severity, with mean K-BILD total scores of 62 (SD 23) and an expected within-subject correlation of 0·8.[30]

For the primary outcome, we used a generalised linear model, assuming a Gaussian family distribution and identity link function, with the difference in HRQOL as the dependent variable and treatment sequence as a fixed effect.[31] In a two-period crossover, carryover (whether pharmacological or psychological) cannot be separated from treatment-by-period interaction.[32] In view of these uncertainties, we took the a-priori decision to adjust for order of treatment[18] to account for the possibility of a difference in effect according to treatment sequence. Unadjusted analysis of the primary outcome is in the

appendix (p 5). Because no obvious differences between baseline variables were apparent according to order of treatment (table 1), and because none of the baseline variables were linked to the primary outcome (appendix p 6), we did not adjust for baseline variables. The study outcome was considered positive if significance at the level of 0·05 (two tailed) was achieved.

The same model was used to analyse differences in SGRQ scores, UCSDSOBQ scores, and 6MWT parameters (except for differences in dyspnoea and fatigue and respective recovery times on the 6MWT, which were analysed with the Koch method for the two-period crossover design[33]). Conditional logistic regression, with sequence as an interaction term, was used to analyse the effects of oxygen on the presence of anxiety or depression. In our analysis of the determinants of the decision to continue on ambulatory oxygen at trial completion, we assumed binary distribution and logit family in logistic regression. We did a a 2×2 χ^2 test to compare the proportion of patients with an improvement with those with a worsening in K-BILD scores greater than the minimal clinically important difference.

Analysis was by intention to treat. Missing data as a result of post-processing incidents (eg, lost questionnaire pages, patient input errors) were less than 1% and were judged to have occurred completely at random. We thus did the analyses both as complete case analyses (ie, omitting missing data) and after replacing missing data with multiple imputation (with 20 replicates imputed by multivariate normal regression over the baseline value of that parameter, the value of global assessment, and the order of treatment). We identified no noticeable or significant differences between the results of these analyses, and thus report only the results of the complete case analysis (ie, without imputed data). Themes emerging from the qualitative interviews were also analysed. All analyses were done with Stata (version 12.1). This trial is registered with ClinicalTrials.gov, number NCT02286063.

Role of the funding source

The study funder had no role in study design; data collection, analysis, or interpretation; or writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between Aug 26, 2014, and Sept 22, 2016, 269 patients were screened. 84 of these screened patients were randomly assigned between Sept 10, 2014, and Oct 5, 2016, 41 to ambulatory oxygen first and 43 to no oxygen first (figure 2). One patient withdrew a few hours after being randomly assigned and did not complete the 6MWT. 37 patients assigned to oxygen first and 39 assigned to no oxygen first completed the trial (figure 2). Baseline characteristics were well balanced between groups (table 1). Mean age overall was 67·9 years (SD 10·4; table 1).

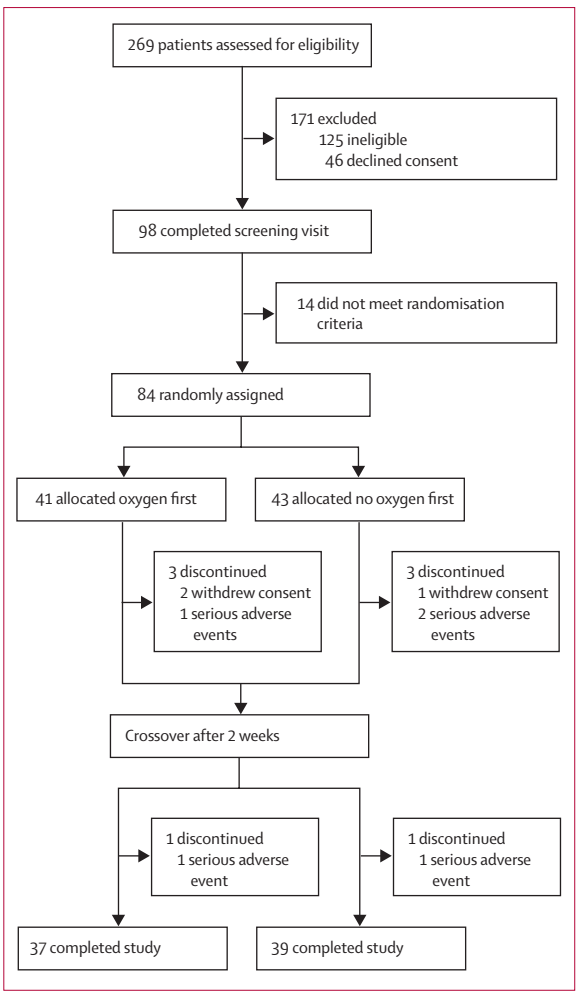

Figure 2: **Trial profile**
Serious adverse events are listed in the appendix (p 9).

26 (31%) patients were women and 53 (63%) had a history of smoking (table 1). The most frequent diagnosis was IPF (49 patients [58%]). 13 (15%) patients had fibrotic hypersensitivity pneumonitis, eight (10%) had connective-tissue-disease-associated interstitial disease, six (7%) had fibrotic non-specific interstitial pneumonia with or without organising pneumonia, three (4%) had unclassifiable interstitial lung disease, two (2%) had fibrotic sarcoidosis, two (2%) had pleuroparenchymal fibroelastosis, and one (1%) had interstitial pneumonitis with autoimmune features. Patients had moderate-to-severe disease, with mean diffusing capacity of the lung for carbon monoxide of 38·5% (SD 9·3) and mean composite physiological index of 52·9 (SD 8·4; table 1). Mean total K-BILD score was 50·5 (11·2). Patients with IPF were older and more likely to be men than were those with other types of interstitial lung disease (appendix p 6). Baseline lung function, questionnaire scores, and 6MWT parameters were similar between patients with and without IPF (appendix p 6).

	Oxygen first (n=41)	No oxygen first (n=43)	Total (n=84)
Sex			
Male	26 (63%)	32 (74%)	58 (69%)
Female	15 (37%)	11 (26%)	26 (31%)
Age, years	68·9 (11·4)	66·8 (9·5)	67·9 (10·4)
Body-mass index	28·5 (5·1)	28·3 (4·6)	28·4 (4·8)
Former smoker	29 (71%)	24 (56%)	53 (63%)
Lung function			
Forced vital capacity, % predicted	71·1 (18·9)	75·1 (19·5)	73·1 (19·2)
FEV_1, % predicted	73·6 (21·0)	76·8 (19·4)	75·2 (20·2)
DLCO, % predicted	39·8 (10·2)	37·3 (8·2)	38·5 (9·3)
Composite physiological index	52·4 (9·1)	53·5 (7·7)	52·9 (8·4)
Screening 6-min walk test on air			
Distance, m	377·1 (122)	367·7 (104·7)	372·4 (113·0)
Peripheral transcutaneous oxygen saturation	84·4 (4·1)	85·7 (3·5)	85·1 (3·9)
Dilated right ventricle on echocardiogram*	6 (16%)	4 (10%)	10 (13%)
Mean BNP (IQR), ng/L	38 (24–61)	29 (17–50)	34 (20–57)
Idiopathic pulmonary fibrosis	23 (56%)	26 (60%)	49 (58%)
K-BILD			
Total	51·2 (8·4)	49·7 (13·4)	50·5 (11·2)
Breathlessness and activities	33·8 (13·6)	34·9 (18·8)	34·4 (16·3)
Chest symptoms	57·4 (16·6)	55·3 (22·8)	56·3 (19·9)
Psychological symptoms	52·1 (10·8)	48·1 (16·7)	50·1 (14·1)
SGRQ			
Total	50·8 (15·1)	51·9 (18·1)	51·4 (16·6)
Symptoms	55·2 (21·9)	56·6 (21·4)	55·9 (21·5)
Activity	69·0 (16·3)	66·6 (19·2)	67·8 (17·8)
Impact	38·7 (18·1)	41·7 (20·6)	40·2 (19·3)
UCSDSOBQ	51·5 (21·2)	48·8 (24·5)	50·1 (22·8)
Hospital Anxiety and Depression Scale†			
Anxiety	9 (22%)	15 (35%)	24 (29%)
Depression	7 (17%)	13 (30%)	20 (24%)

Data are mean (SD) or n (%),unless otherwise specified. DLCO=diffusing capacity of the lung for carbon monoxide. BNP=brain natriuretic peptide. K-BILD=King's Brief Interstitial Lung Disease Questionnaire. UCSDSOBQ=University of California, San Diego Shortness of Breath Questionnaire. SGRQ=St George's Respiratory Questionnaire. *n=38 for the oxygen first group and 40 for the no oxygen first group. †n (%) of cases with anxiety and depression scores ≥8 are presented.[28,29]

Table 1: **Baseline characteristics of randomly assigned patients**

For the placebo-controlled 6MWT, the median Borg dyspnoea score at the end of the test was 2·1 (IQR 0·7–3·4) in patients on supplemental oxygen and 3·0 (IQR 2·0–5·1) in those on placebo air (p<0·0001; table 2). Participants on supplemental oxygen walked a mean of 18·5 m (95% CI 10·9–26·1) farther than those on placebo oxygen (p=0·001; table 2). Compared with placebo air, oxygen was also associated with significant reductions in the dyspnoea score and fatigue recovery time after the 6MWT (table 2).

In the primary outcome analysis, compared with use of no oxygen, ambulatory oxygen used during daily activities for 2 weeks was associated with significant improvements in total K-BILD scores [55·5 (SD 13·8) on oxygen *vs* 51·8 (SD 13·6) without oxygen; adjusted mean difference 3·7 [95% CI 1·8–5·6]; p<0·0001; figure 3; table 3). Scores for the breathlessness and activity and chest symptoms subdomains of K-BILD were also significantly higher in the oxygen group than in the no oxygen group, but scores on the psychological symptoms subdomain did not differ significantly between groups (figure 3; table 3). The difference in K-BILD total scores between groups did not seem to be affected by order in which the patients received the intervention (appendix p5). After 2 weeks of ambulatory oxygen, 13 (18%) of 74 patients had an improvement in total K-BILD scores of greater than 8, 27 (36%) had an improvement of greater than 4, and two (3%) had deteriorations in K-BILD scores of greater than 8 (p=0·003). None of the baseline clinical characteristics significantly affected the change in K-BILD total score (appendix p 6). Furthermore, we noted no significant associations between change in total K-BILD scores and K-BILD scores at baseline (appendix p 7). Changes in K-BILD total scores remained significant (p<0·0001) after adjustment for study site (data not shown).

Patients reported significantly reduced breathlessness and improved walking ability after 2 weeks of ambulatory oxygen compared with no oxygen (p<0·0001 for both; figure 4). 52 (68%) of 76 patients reported reduced breathlessness on oxygen and only one (1%) reported increased breathlessness. By contrast, 18 (24%) patients deteriorated in the no oxygen group, and only one improved. Significant improvements after 2 weeks of ambulatory oxygen (compared with no oxygen) were also noted for UCSDSOBQ scores (adjusted difference –8·0 [95% CI –12·4 to –3·6]; p<0·0001) and SGRQ total scores (adjusted difference –3·6 [95% CI –6·7 to –0·6]; p=0·018), with the largest difference noted in the activity domain (table 3). No significant differences were noted in terms of the numbers of patients meeting the HADS thresholds for depression or anxiety (table 3).

Eligible data from SenseWear Pro Armbands were available for 41 patients (appendix p 8). According to established thresholds[35] for physical activity levels, 28 (68%) participants were very inactive (ie, physical activity level <1·4), and only two (5%) could be categorised as active (ie, physical activity level >1·7). Activity levels and step counts did not differ significantly between the ambulatory oxygen and no oxygen periods (appendix p 8). In assessments of the relation between changes in 6MWT parameters on oxygen versus placebo air and the primary outcome, we noted no significant associations (appendix p 8).

Median patient-reported cylinder use per week was 2·75 cylinders (IQR 1·59–4·28; range 0–14), and the median oxygen flow rate was 3 L/min (IQR 2·5–5·0; range 1–6). Independent reports from the oxygen companies or clinicians completing domiciliary visits were available for 47 patients. In these participants, median self-reported oxygen use (2·4 cylinders

	Oxygen	Placebo air	Mean difference (95% CI)	Median difference (IQR)	p value
SpO_2 at end of test	90·6 (5·7)	84·7 (4·7)	5·9 (4·8 to 7·0)	..	<0·0001
Minimum SpO_2	88·9 (4·3)	82·9 (4·4)	5·9 (4·8 to 7·1)	..	<0·0001
Distance walked, m	373·2 (89·9)	354·7 (97·8)	18·5 (10·9 to 26·1)	..	0·001
Heart rate at end of test	99·9 (14·3)	102 (18·3)	−2·2 (−4·9 to 0·6)	..	0·12
Maximum heart rate	104·4 (13·8)	108·9 (15)	−4·5 (−6·2 to −2·8)	..	0·01
SpO_2 recovery time, s	117 (101)	217·7 (124)	−101 (−129 to −73)	..	<0·0001
Heart rate recovery time	163·7 (138·7)	191·9 (145·3)	−28·2 (−67·9 to 11·5)	..	0·06
Borg dyspnoea score	2·1 (0·7 to 3·4)	3·0 (2·0 to 5·1)	..	−1·6 (−2·1 to −1·1)	<0·0001
Borg fatigue score	0·0 (0·0 to 1·4)	0·1 (0·0 to 2·6)	..	−0·4 (−1·1 to −0·2)	<0·0001
Borg dyspnoea score recovery time, s	112 (72 to 164)	171 (114 to 229)	..	−49 (−99 to −1)	0·0008
Borg fatigue score recovery time, s	0 (0 to 82)	0 (0 to 174)	..	−14 (−64 to −0·5)	<0·0001

Data are mean (SD) or median (IQR). SpO_2=transcutaneous arterial oxygen saturation.

Table 2: **Effects of oxygen *vs* placebo air on 6-minute walk test parameters**

[IQR 2·0–4·3; range 0·5–14·0]) was similar to that recorded in independent reports (2·3 cylinders [IQR 0·5–3·5; range 0·0–14·0]; concordance correlation coefficient 0·87; appendix p 2).

At the end of the trial, 51 (67%) of 76 patients chose to continue using ambulatory oxygen. Younger age and more severe lung impairment (as shown by the composite physiological index) were significantly associated with this decision in univariable (p=0·002 and p=0·008, respectively; appendix p 9), and bivariable (p=0·009 and p=0·037, respectively) analyses.

In terms of trial outcomes, in univariable analyses, the most significant determinants of the decision to continue using ambulatory oxygen were patients' global assessment of change in breathlessness (odds ratio 4·1 [95% CI 1·8–9·4]; p=0·001) and walking ability (3·2 [1·5–6·9]; p=0·003; appendix p 9). In multivariable analyses, patients' global assessment of change in breathlessness (or in a separate model the assessment of changes in walking ability) remained the strongest determinant of the decision to continue on oxygen, and younger age also remained independently predictive (appendix pp 9–10).

The most common adverse events were upper respiratory tract infections (three in the oxygen group and one in the no-treatment group). Five serious adverse events were recorded during the trial, two (including one death) in the 2 weeks on oxygen and three (including one death) in the 2 weeks of no oxygen. All adverse events were classified as unrelated to the trial (appendix p 10).

21 of the 56 trial participants at the Royal Brompton site (and three carers) agreed to participate in qualitative interviews (appendix p 4). 18 interviews were done at the hospital, and three in participants' homes. Seven themes arose from the interviews: attitudes about use of ambulatory oxygen, benefits of ambulatory oxygen, use of ambulatory oxygen indoors, use of ambulatory oxygen outdoors, challenges faced, supply of oxygen, and support given (table 4). Although most patients reported

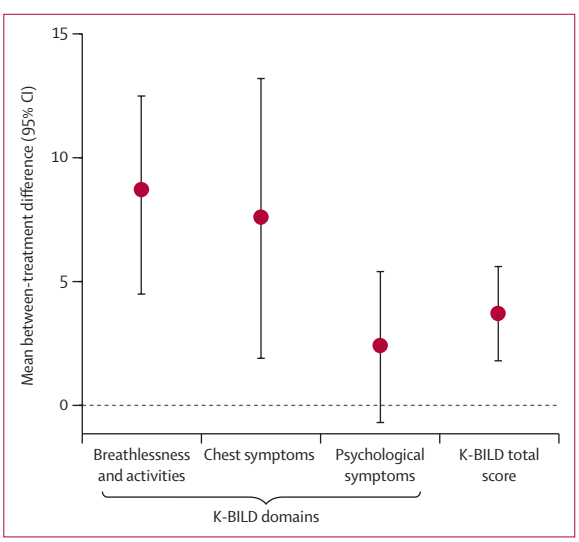

Figure 3: **Mean difference in K-BILD scores between ambulatory oxygen and no treatment, adjusted for order of treatment**
K-BILD=King's Brief Interstitial Lung Disease Questionnaire.

initial apprehension about use of oxygen, 15 patients' attitudes changed when they experienced improved exercise tolerance and quality of life. 16 patients continued with oxygen after the trial. Six people who were initially frightened or shocked at the prospect of using ambulatory oxygen had persistent negative impressions of the treatment, and five stopped oxygen after the trial.

20 patients experienced benefits from ambulatory oxygen, including less breathlessness when walking or doing daily activities (n=16), not having to stop as much when doing activities (n=13), and reduced cough (n=7). They reported that their quality of life improved because they could do more (n=15). Patients reported less chest tightness, reduced fatigue, increased energy, less dizziness, and feelings that supplemental oxygen provided a "boost" when they were "feeling low". All

	Oxygen	No oxygen	Mean between-treatment difference (95% CI)	p value
K-BILD* (n=74)				
Total	55·5 (13·8)	51·8 (13·6)	3·7 (1·8 to 5·6)	<0·0001
Breathlessness and activities	44·4 (22·6)	35·8 (20·4)	8·6 (4·7 to 12·5)	<0·0001
Chest symptoms	65·5 (25·2)	57·9 (29·2)	7·6 (1·9 to 13·2)	0·009
Psychological symptoms	55·2 (19·6)	52·8 (19·6)	2·4 (–0·6 to 5·5)	0·12
UCSDSOBQ† (n=72)	41·0 (30·5)	49·1 (34·1)	–8·0 (–12·4 to –3·6)	<0·0001
SGRQ† (n=72)				
Total	48·7 (25·3)	52·4 (25·0)	–3·6 (–6·7 to –0·6)	0·018
Activity	61·5 (27·3)	68·9 (25·2)	–7·5 (–12·4 to –2·5)	0·003
Symptoms	53·3 (30·7)	54·9 (31·9)	–1·7 (–6·6 to 3·3)	0·51
Impact	39·7 (28·6)	41·8 (28·8)	–2·1 (–5·6 to 1·3)	0·22
Hospital Anxiety and Depression Scale‡ (n=70)				
Anxiety score ≥8	16 (23%)	18 (26%)	0·60 (0·14 to 2·50)§	0·47
Depression score ≥8	10 (14%)	18 (26%)	0·14 (0·02 to 1·16)§	0·14

Data are adjusted mean (SD) or n (%). K-BILD=King's Brief Interstitial Lung Disease Questionnaire. UCSDSOBQ=University of California, San Diego Shortness of Breath Questionnaire. SGRQ=St George's Respiratory Questionnaire. *Higher scores reflect better quality of life; minimal clinically important difference estimates for K-BILD scores are 4 (range 3·7–4·2) for total score, 6 (5·6–6·5) for breathlessness and activities score, 5·4 (4·6–6·9) for psychological symptoms score, and 0·5 (SD 8·9) for chest symptoms score.[34] †Lower scores reflect better quality of life. ‡Higher scores reflect higher depression and anxiety. §Data are odds ratio (95% CI), calculated on the basis of conditional logistic regression.

Table 3: **Quality-of-life, shortness-of-breath, and anxiety and depression scores after 2 weeks on and 2 weeks off ambulatory oxygen**

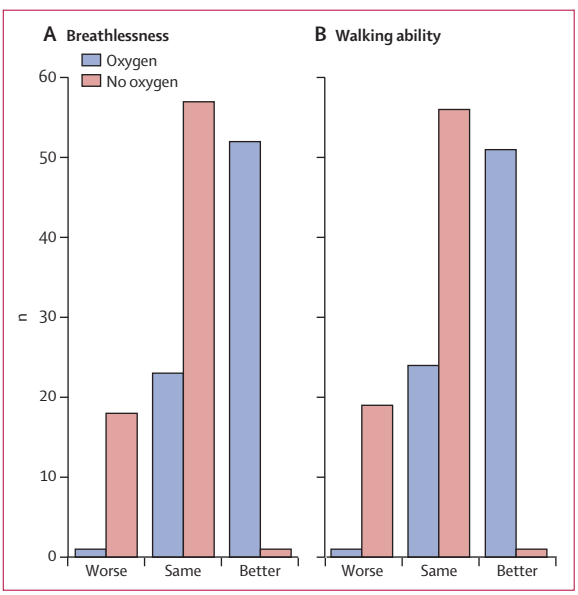

Figure 4: **Numbers of patients reporting improved, same, or worse breathlessness (A) and walking ability (B) after 2 weeks on ambulatory oxygen or no treatment**
The wording of the questions is provided in the appendix (p 3).

three carers reported that their spouses benefited from the treatment and continued to use ambulatory oxygen. Only one patient reported little benefit from using ambulatory oxygen.

Ambulatory oxygen was reported to be helpful indoors with tasks that required some exertion, such as housework, DIY, and going upstairs. Most used ambulatory oxygen outdoors to go for walks, garden, shop, socialise, walk to work, and get to and from public transport. Some respondents reported feeling increased confidence to go on outings. However, the amount used outdoors varied, with some patients using oxygen most times they went out and some using oxygen rarely or not at all because of the particular challenges involved in use outside the home.

Cylinders were cumbersome or awkward to carry for some patients, and two of the three carers found the cylinders heavy. A few patients and one carer also worried that cylinders would run out, which could be a particular challenge if they were away from home. Three of the four patients who worked encountered workplace challenges, including an initial reluctance among employers to accommodate oxygen use. Visibility of the ambulatory oxygen was also a concern for ten participants. However, most patients used ambulatory oxygen despite these concerns because of the perceived benefits.

Oxygen treatment had prognostic significance for four patients, because it made them question if their illness was getting worse. One carer saw oxygen therapy as "a sign that he is being even more not well", but when she realised that oxygen was helping to make him feel better, she was happy for him to continue (carer 16a, wife). The patients who did not continue with ambulatory oxygen after the trial reported more challenges than did patients who continued treatment.

A few patients and one carer reported feeling shocked when the first delivery of oxygen cylinders arrived. However, overall, very few problems were reported with oxygen delivery and supply, and patients reported receiving good support and information. All patients and carers seemed to particularly gain from the support related to oxygen use provided by the research coordinator throughout the trial.

Discussion

To our knowledge, this study is the first randomised controlled trial of the effects of ambulatory oxygen on day-to-day HRQOL in patients with fibrotic interstitial lung disease. Ambulatory oxygen was associated with improvements in total K-BILD scores compared with no treatment. Ambulatory oxygen use was also associated with significant improvements in scores on the breathlessness and activity and chest symptoms subdomains of K-BILD, in UCSDSOBQ scores, and in global assessments of change in breathlessness and walking ability (key secondary outcomes), but not the psychological symptoms domain of K-BILD. Analysis of qualitative interviews with participants showed that almost all interviewed patients thought that oxygen was beneficial but was associated with challenges including visibility, the perceived prognostic significance, and work-related issues.

The mean improvement in K-BILD total score was below the previously reported minimal clinically important

difference estimate of 8.[30] This estimate was originally calculated in a cohort of 57 patients with interstitial lung disease, who had, on average, milder disease than patients in our trial, who had disease severe enough to cause desaturation to 88% or less on exertion. In advanced interstitial lung disease, the ability to detect major differences is likely to be reduced because of the severity of disease and the confounding effect of complications and comorbidities. In a subsequent larger study[34] of 157 patients with interstitial lung disease of similar severity to that of the patients in AmbOx, the minimal clinically important difference for the K-BILD total score was 4·0 (range 3·7–4·2), although so far these data have been released only as a conference abstract and not in a peer-reviewed publication. The mean difference of 3·7 between groups in the K-BILD total score in our trial is thus at the lower end of the range of this revised minimal clinically important difference, and further studies are needed to show whether ambulatory oxygen is associated with a change that is clinically meaningful to patients. Nonetheless, the K-BILD difference was greater than 8 in 18% of patients, and greater than 4 in 36%, a noteworthy improvement in view of the absence of treatments that improve quality of life in progressive pulmonary fibrosis. The findings of the qualitative interviews done at the end of the study also suggest a clinically important benefit. Most interviewed patients described symptomatic improvement in several areas despite the challenges posed by use of ambulatory oxygen. Taken together, these findings suggest that the improvement in the K-BILD total score reflects a change that is relevant in patients' daily lives, although further studies are clearly needed to support the clinical importance of our findings.

Within K-BILD, the most substantial improvements were in breathlessness and activity scores, with a mean between-treatment difference of 8·6—substantially higher than the minimal clinically important difference of 6 for this subdomain.[34] The K-BILD total score amalgamates items relating to general quality of life and lung-specific symptoms. An intervention is quite likely to improve some subdomains more than others, particularly if it is used only during exertion. The breathlessness and activity subdomain includes four questions that are focused on breathlessness during exertion and when carrying weights, and on how often patients' lung conditions lead to avoidance of tasks or interfered with work or daily tasks. Ambulatory oxygen would be expected to mostly affect breathlessness and activities, and that the largest effects were noted in this subdomain rather than in the total score—which also includes questions about patients' psychological response to their illness that would not necessarily be affected by a short-term intervention used only during activities—is unsurprising. The improvements in the breathlessness and activities subdomain are particularly relevant to patients with pulmonary fibrosis, in which breathlessness is the symptom most strongly linked to quality of life.[4,5]

	Patient
Attitudes to using ambulatory oxygen	
"Initially I thought 'it is going to be strange' … [I was] a bit self-conscious with tubes hanging out of [my] nose and face and having to carry it around, but I had got to the stage where in my job I was so incapacitated. I was beginning to think that I was going to have to leave my job, and that would have broken my heart, and when I got the oxygen all of a sudden it has all changed. I can do what I used to do. I can walk up the stairs and talk to somebody when I get to the top. I can even sit and sing now; I couldn't sing for ages."	Patient 09 (male, 62 years old)
"I only went on the oxygen because of this trial. I didn't want it, to be honest with you. It frightened me. No, I didn't like the idea of it, but I thought because I am getting more attention, better help, I will give it a go."	Patient 17 (female, 54 years old)
Benefits of ambulatory oxygen	
"Freedom. Being able to do things I haven't been able to do for such a long time. It made me feel less tired. It made me feel less breathless. My cough wasn't so bad. I could do things without having to stop. It taught me how much this disease has stopped me from doing things. It's not because I don't want to do them—I'd love to do them—it's the fact that I physically, because of the breathlessness, can't do it."	Patient 20 (female, 52 years old)
"It was definitely helpful because when I am normally hoovering, I have to take it steady or perhaps stop for a couple of minutes, then I carry on and do it. With oxygen, I could just do the whole lot."	Patient 18 (male, 70 years old)
Use of ambulatory oxygen indoors	
"Playing with the grandkids is the same. I can carry on with it. Before I would not have been able to do very much … breathing is a lot easier."	Patient 08 (male, 70 years old)
Use of ambulatory oxygen outdoors	
"If I was digging, I would have to stop after 10 min to have a breather, but with oxygen I could carry on and carry on."	Patient 08 (male, 70 years old)
"I didn't cough quite as much and gasp for breath, and I did go out more, whereas when I'm not on oxygen, I tend to avoid going out."	Patient 21 (female, 65 years old)
Challenges of using ambulatory oxygen	
"Although you are benefiting from the oxygen, having to carry a heavy cylinder kind of defeats the object a little bit."	Patient 02 (male, 57 years old)
"I had to have a full health-and-safety risk assessment before I was allowed to take it into work, then every time I left the office, I had to take the oxygen with me—so that was very difficult."	Patient 10 (female, 52 years old)
"I just felt embarrassed for having these tubes running up my nose and from a tank on my back. If it was a pill, nobody notices it, but with a cylinder on your back and a plastic tube up your nose it is much more visible."	Patient 16 (male, 69 years old)
"[At the] End of the road, you get [given] the oxygen and you think, because the last 8 years I never had oxygen, but then, all of a sudden, you get the oxygen and you feel 'is it time [to die]? Is it time I am going to go?' It is that feeling."	Patient 03 (male, 68 years old)
Supply of ambulatory oxygen	
"The first day the oxygen arrived to the house, I felt terrible. I was expecting one bottle of oxygen, he brought eight … it knocked me back a bit."	Patient 03 (male, 68 years old)
"It was good, they [the oxygen suppliers] gave me leaflets to explain everything and they explained as well. They explained everything: how to use it, and if any problems, call them."	Patient 11 (male, 53 years old)
Support given	
"Research coordinator has been very good and has explained everything. She has been wonderful."	Patient 05 (female, 69 years old)

Table 4: **Patient quotes showing the main themes derived from qualitative interviews**

The real clinical benefits of an intervention could be better captured by patients' individual judgments than by a one-size-fits-all minimal clinically important difference. In this regard, 52 of 76 patients reported improved breathlessness at the end of the 2 weeks on oxygen, compared with only one patient after 2 weeks with no oxygen. Ambulatory oxygen was also associated with significant improvements in the other key secondary outcome, UCSDSOBQ scores. The mean between-group difference of 8 in scores was higher than the minimal

clinically important difference reported for patients with COPD (>4).[36] Although the minimal clinically important difference has not been tested in interstitial lung disease, our findings for the UCSDSOBQ, a questionnaire dedicated to breathlessness across a range of activities, further suggest that ambulatory oxygen has a clinically beneficial effect. Ambulatory oxygen use was not significantly associated with HADS scores—an unsurprising finding in view of the short duration of the intervention that is in keeping with the non-significant findings for the K-BILD psychological domain. The improvements noted in the SGRQ total score, although significant, were less substantial than those in K-BILD or UCSDSOBQ scores. The biggest improvement was noted in the activities subdomain, in keeping with the findings for the K-BILD breathlessness and activity subdomain. Furthermore, most patients chose to continue using ambulatory oxygen after the trial.

Despite improved breathlessness and quality of life scores, we noted no significant differences in step counts or physical activity between the oxygen and no-oxygen periods. However, analysis of SenseWear activity data was hampered by technical or logistic difficulties, as a result of which analysable data were available for only 41 patients. This small sample could have limited our power to detect an effect, and further studies focused on the effects of ambulatory oxygen on activity levels are needed before any definitive conclusions can be drawn.

This study has several potential limitations. The study design did not include a placebo group, although this decision was carefully reached. Ambulatory oxygen cannot be administered without the concomitant weight of the oxygen delivery device. The intervention is a combination of possible benefits from oxygen and the disadvantages of canister weight. In a study[37] of 27 patients with COPD, 25 (93%) reported that the weight of the oxygen system was a key negative issue. Cylinder weight was also a consistent issue identified in our qualitative interviews. The negative effects of a placebo cylinder would mean that a comparatively positive result in the ambulatory oxygen group would be clinically difficult to interpret. The placebo treatment would be actively harmful to study participants, and carrying an air-filled canister would be expected to lead to reduced exercise tolerance. As such, we concluded that the use of an air-filled cylinder group would not provide a better comparator group for ambulatory oxygen than would no intervention. In view of the absence of a placebo group, independent checks on the amount of oxygen used by patients were done. The good agreement between self-reported number of cylinders used and independent reports by oxygen companies or specialist nurses during home visit suggests that self-reported use of oxygen cylinders was a reliable measure. The crossover design of the trial means that we cannot exclude a potential carryover effect of oxygen in patients who were randomly assigned to start oxygen first. Such a carryover could be related to a longer than expected biological effect of oxygen on tissues, psychological effects, or differences in the perception of change depending on whether there is improvement or worsening, as suggested by Redelmeier and colleagues.[38]

Although data entry for the primary and key secondary outcomes was done independently by an assessor masked to any trial information, and the questionnaires were filled in by patients independently, the researchers collecting the questionnaires were not masked to treatment, and could have introduced bias. Another limitation of the study is that, in view of its short duration, the potential for long-term harm of supplemental oxygen via oxidative stress in the lungs[39]—or conversely long-term benefits as a result of the oxygen radical production induced by intermittent periods of hypoxia[40]—was not assessed. Future studies of supplemental oxygen use in interstitial lung disease should include measurements of oxidative stress markers to assess these possibilities further.[41]

The beneficial effect of supplemental oxygen on breathlessness could be because of stimulation of the upper airway mucosa receptors by the high air flow rather than the oxygen itself.[42,43] In a study[42] of breathless patients with chronic lung disease who were not hypoxic at rest by Abernethy and colleagues, in which ambient air and oxygen were delivered via nasal cannulae at a flow of 2 L/min continuously for 7 days, no difference was noted between treatments in the effects on dyspnoea. However, their cohort mostly comprised patients with COPD, and only 6% of participants had interstitial lung disease. Furthermore, oxygen was provided irrespective of activities, was not titrated to optimise oxygen saturation on exertion, and the breathlessness scores seemed to be measured at rest. Conversely, Leach and colleagues[19] compared 6MWT distance and breathlessness scores in patients with severe lung disease between walking tests done using a sham cylinder containing air at a flow rate of 4 L/min or oxygen cylinders with flow rates of 2 L/min, 4 L/min, and 6 L/min in random order. All patients, including patients with interstitial lung disease, who were analysed separately from those with COPD, experienced significant worsening in distance walked and in visual breathlessness scores when they carried the extra weight of the cylinder of placebo air, despite the nasal cannulae air flow of 4 L/min, whereas the distance walked and breathlessness scores progressively improved with increasing oxygen flow rates.

However, in a meta-analysis[11] of two placebo-controlled studies published in 2017, short-term supplemental oxygen during short bursts of exercise was associated with improvements in exercise performance but had inconsistent effects on breathlessness. Our study included a 6MWT on oxygen versus on placebo air provided at the same flow and titrated to the needs of the individual patient. Breathlessness was significantly improved by oxygen compared with placebo air, with a median decrease in the Borg dyspnoea score by roughly one unit, although the acute effects of oxygen might not

necessarily translate into beneficial effects in day-to-day life. Furthermore, the reduced sensation of breathlessness associated with oxygen might not solely be because of improved oxygenation in peripheral tissues. Nevertheless, taken together, these data suggest that the benefit noted with supplemental oxygen in this study is dependent on oxygen itself rather than the effect on nasal mucosa receptors of high flows of air, although further studies directly comparing the two modalities with a placebo air group would be useful. One such study is underway (ACTRN12617000054314) comparing ambulatory oxygen with placebo air, and its findings should usefully complement ours.

In AmbOx, ambulatory oxygen was associated with improved HRQOL in patients with interstitial lung disease who experience substantial desaturation on exercise. The captured experiences of patients and carers in this mixed-methods study add to knowledge of patients' and carers' experiences of ambulatory oxygen in their private and public social worlds. Patients mostly reported improvement of symptoms and quality of life, supporting the quantitative findings of the trial. However, even if oxygen improved symptoms, patients and their carers still encountered physical and psychosocial challenges in using ambulatory oxygen, as has been reported in other studies.[15,16] Roughly a third of patients decided not to continue using ambulatory oxygen after our trial, which suggests that the challenges associated with supplemental oxygen use should be further assessed. Our qualitative findings show that most patients were initially concerned about using oxygen, but the perceived benefits meant that most became more positive and opted to continue. However, a few patients had persistently negative impressions of ambulatory oxygen, almost all of whom chose not to continue treatment after the trial, despite reporting symptomatic benefits. Some of the challenges reported by patients who decided not to continue using ambulatory oxygen were the prognostic significance attributed to having oxygen prescribed, challenges encountered in the workplace, and concerns about social stigma. These specific concerns could be areas for potential intervention and provision of specific support.

Younger age was associated with an increased likelihood of continuing to use ambulatory oxygen. Whether this association is related to higher motivation to remain active in younger patients or other factors will also require further study. The strong association between global assessment of change responses—ie, a simple question about whether patients had noticed a change in breathlessness or walking ability, or both, after 2 weeks on ambulatory oxygen—and continuation of oxygen suggests that a trial period of 2 weeks could be useful to assess whether the benefits provided by ambulatory oxygen overcome the burden associated with use. Further trials of 2 weeks' duration would allow clarification of the many questions that arise from oxygen use, and could help to focus resources on patients who are most likely to continue to use oxygen long term. We also propose an economic assessment of the cost-effectiveness of ambulatory oxygen in improving HRQOL, to establish the value of introducing the treatment more broadly.[18]

In conclusion, ambulatory oxygen use was associated with reduced exertional hypoxia and dyspnoea on 6MWTs and seemed to improve HRQOL in patients with fibrotic interstitial lung disease, a group of diseases associated with life-changing respiratory symptoms for which few beneficial interventions are available. Whether other compressed gases, including air, can provide similar benefits, and whether the improvements noted with ambulatory oxygen are sufficient to be clinically meaningful to patients, will require further study. Despite the downsides of supplemental oxygen, most patients chose to continue using ambulatory oxygen, suggesting an overall positive effect. Nevertheless, further studies are needed to better assess the effects of ambulatory oxygen and ultimately to allow the development of specific guidelines for ambulatory oxygen use in patients with interstitial lung disease.

Contributors

DV, LGS, MF, PSe, AUW, and EAR designed and planned the study, which was supervised by EAR. DV, LM, AF, VA, SC, ADL, AM, CH, AS, MP, JB, FC, PMG, PLM, GAM, MK, VK, AMR, HA, LGS, and PSa participated in recruitment and data collection. VT monitored the study and supervised data entry. SF, AF, and MF collected and analysed qualitative interviews. MBonin was the independent data enterer for the primary and secondary outcomes. MJP and NSH contributed to the SenseWear Pro Armband data analysis. PSe, MBonif, MJP, CB, CJWS, SSB, TMM, PC, NSH, JAW, and AUW contributed to the analytic approach. PSe and WB did the statistical analysis. EAR wrote the Article, with input from all authors.

Declaration of interests

PMG reports personal fees and other fees from Boehringer Ingelheim and Roche outside of the submitted work. PLM and his employing institution have received speaker fees from Roche outside of the remit of the submitted work. MK reports personal fees from Roche and Intermune outside of the submitted work. AMR reports grants and personal fees from Hoffmann La Roche outside of the submitted work. SSB reports personal fees from Patara and Novartis and other fees from Chiesi and Boehringer, outside of the submitted work. TMM has, via his institution, received industry–academic funding from GlaxoSmithKline R&D and UCB, and has received consultancy or speaker fees from Apellis, AstraZeneca, aTyr Pharma, Bayer, Biogen, Boehringer Ingelheim, Galapagos, GlaxoSmithKline R&D, Indalo, Pliant, ProMetic, Roche, Samumed, and UCB. AUW reports lecture or advisory board fees from Boehringer Ingelheim, Roche, and Bayer outside of the submitted work. EAR has received consultancy or speaker fees from Hoffmann La Roche, Boehringer Ingelheim, and Mundipharma outside of the submitted work. All other authors declare no competing interests.

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