Eur Respir J 2008; 31: 1114–1124
DOI: 10.1183/09031936.00116707

SERIES "COMPREHENSIVE MANAGEMENT OF END-STAGE COPD"
Edited by N. Ambrosino and R. Goldstein
Number 4 in this Series

Drugs (including oxygen) in severe COPD

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ABSTRACT: Access to comprehensive guidelines on the management of chronic obstructive pulmonary disease (COPD) is now available, and several treatment goals of therapy have been identified from these guidelines, which have since been studied in clinical trials.

Drug therapy is a key component of an individual patient's management plan, particularly in more severe disease. During the past few years, a number of new drug treatments have become available, although these are not always appropriately prescribed; this is particularly the case for oxygen.

For patients with a history of exacerbations, there is good evidence for the use of inhaled long-acting anticholinergic agents or combined inhaled steroids and long-acting β-agonists. Evidence for prophylactic antibiotics and antioxidant agents is lacking. Nutritional and calorie supplementation have not been shown to improve exercise capacity. Statins may improve outcomes in COPD, but prospective trials are needed to confirm this.

The evidence for the use of long-term oxygen therapy in hypoxaemic patients is robust. Ambulatory oxygen improves exercise capacity, but whether it is used appropriately is in doubt. Overall, short burst oxygen therapy does not offer a benefit and therefore cannot be recommended.

KEYWORDS: Chronic obstructive pulmonary disease, combining, oxygen, drug therapy, exacerbation

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Received:
October 05 2007
Accepted after revision:
October 25 2007

STATEMENT OF INTEREST
Statements of interest for all authors of this manuscript can be found at www.erj.ersjournals.com/misc/statements.shtml

As chronic obstructive pulmonary disease (COPD) progresses, most patients are treated with some form of pharmacological therapy, either acutely when they have a symptomatic exacerbation or chronically to reduce persisting symptoms and/or prevent future exacerbations or complications developing. Most, but not all, of these therapies have been ''borrowed'' from the management of asthma, reflecting the common features of airflow obstruction and airway inflammation. However, the results of treatment are very different, as are the expectations of success, in a condition traditionally defined by having only a partial response to treatment. In the current article, supplemental oxygen (O_2) will be included as a prescribed drug.

The last 10 yrs has seen a rapid growth in the number of treatment studies in COPD. Longer reviews of this topic are available, as are summaries of treatment guidance [1, 2]. Most studies have involved patients with severe-to-very-severe disease (forced expiratory volume in one second (FEV_1) <50% predicted by the American Thoracic Society/European Respiratory Society criteria [3]). Disease severity is not always closely linked to post-bronchodilator spirometry, although a general relationship applies in large populations. Thus, patients with very poor health status may have an FEV_1 of 55% pred, whilst a patient with an FEV_1 of only 35% pred may have relatively few symptoms. Similarly, exacerbations and hospitalisations become more frequent as COPD progresses and are also markers of a poor prognosis [4], although lung function in nonventilated COPD patients who are hospitalised is not necessarily as severely impaired as one would imagine [5, 6]. Finally, respiratory failure can develop in patients with an FEV_1 >30% pred. Therefore, although FEV_1 impairment reflects disease severity, it should not be the only criterion for which drug therapy is prescribed.

Previous articles in this series: No. 1: Viegi G, Pistelli F. Sherrill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. *Eur Respir J* 2007; 30: 993–1013. **No. 2:** Fabbri LM, Luppi F, Beghé, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008; 31: 204–212. **No. 3:** Hill K, Geist R, Goldstein RS, Lacasse Y. Anxiety and depression in end-stage COPD. *Eur Respir J* 2008; 31: 667–677.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

Table 1 is a modified summary of the Global Initiative for Chronic Obstructive Lung Disease goals of therapy in chronic disease. The different classes of drugs commonly used and the doses given are listed in table 2. O_2 therapy is addressed separately.

DRUG THERAPY FOR THE HOSPITALISED PATIENT

Hospitalised COPD patients are given much the same drug therapy as they were 25 yrs ago. Maintaining tissue O_2 delivery without inducing carbon dioxide (CO_2) retention is still the goal of controlled O_2 therapy [7]. Nasal prongs are less likely to dislodge from the face of the patient than masked O_2 [8], but are less precise for delivering a specific inspired O_2 concentration [9]. Nebulised bronchodilators, usually a combination of high-dose β-agonists and anticholinergics, are now widely used. Such a combination improves operating lung volumes more than either drug alone in stable disease [10], and has similar effects in acute disease, although these may take some time to become apparent (fig. 1) [5]. Intravenous theophylline preparations do not improve lung function when given together with nebulised bronchodilators [11, 12], but do lower arterial CO_2 tension slightly. The benefits of this are probably outweighed by the risk of toxicity and the availability of effective ventilatory support with noninvasive ventilation [13]. Antibiotics probably reduce exacerbation duration when given to outpatients [14], but there is limited information regarding their use in hospitalised patients with COPD. One exception is the study of ofloxacin on mechanically ventilated COPD patients in North Africa, where there was a reduced occurrence of pneumonia in patients treated prophylactically with this drug [15]. Oral corticosteroids given for 7–10 days in a dose of ~0.6 $mg \cdot kg^{-1}$ improve lung function, reduce hospital stay and reduce the risk of treatment failure and relapse (fig. 2) [16, 17]. Care must be taken not to prolong oral corticosteroid therapy, given the known adverse effects of these drugs.

DRUGS AND THE SECONDARY PREVENTION OF COPD

There are major benefits in smoking cessation. Knowledge that the person has airflow obstruction increases their likelihood of stopping, at least early in the disease [18, 19]. Data from the Lung Health Study [20] showed that, in mild disease, the use of nicotine replacement therapy and advice translated into an improvement in longer term mortality, although this may not apply when COPD is well established. Patients receiving bupropion did quit more often than those offered standard advice [21], and data with varenicline are awaited, as this was superior to bupriopion when compared in healthy smokers [22].

Long-term studies on the effects of anti-inflammatory drugs, such as inhaled corticosteroids and *N*-acetylcysteine, on the rate of decline of FEV1 have reported negative results [23–26], and a meta-analysis of inhaled corticosteroids has produced conflicting claims regarding their effect on lung function decline [27, 28]. Data presented in abstract form suggest that bronchodilators and inhaled corticosteroids, either alone or in combination, may slow the rate of decline in FEV1, but a fuller presentation of this information is needed before this can be accepted [29].

IMPROVING RESTING LUNG MECHANICS

Improvement in lung function assessed by the FEV1 has been accepted for many years, although the relationship between health status and symptoms is now recognised as being weaker than first thought. Reliance on ''as needed'' therapy is not appropriate in COPD [30], and the major benefit of long-acting inhaled bronchodilators is not due to an increase in potency but to duration of action [31]. Both β-agonists and anticholinergics abolish resting airway tone and improve airflow during extended periods of use [32, 33]. Combining these drugs produces the following additional benefits. In general, oral theophylline is a weakly effective bronchodilator and has more side-effects at pharmacological doses [34]. Inhaled corticosteroids produce a small improvement in post-bronchodilator FEV1 comparable with that due to long-acting β-agonists (LABA) in some [35], but not all [36], clinical studies. These effects are sustained over 3 yrs [37]. In general, improvement in spirometry is associated with reduced lung volumes, particularly residual volume and functional residual capacity [38], without necessarily changing the FEV1/forced vital capacity ratio [39]. These changes in operating lung volumes are particularly important in predicting improvements in exercise performance.

EXERCISE CAPACITY

Exercise performance and the accompanying effort-induced breathlessness are important independent predictors of mortality and hospitalisation in COPD [40, 41]. Improvements in spirometry do not predict changes in exercise capacity [39, 42], but the reduction in end-expiratory lung volume post-bronchodilator explains the increase in exercise duration and delay in reaching peak levels of breathlessness. This is seen with both major classes of long-acting inhaled bronchodilators in severe COPD [43, 44]. Not all patients improve their exercise performance, at least after short-acting β-agonists [45], and this may reflect differences in the behaviour of the chest wall when patients change their breathing strategy after a bronchodilator [46]. Similar improvements in exercise capacity have been seen with the combination of an inhaled corticosteroid and LABA, with the effects of the combination drug occurring relatively early after administration and affecting lung volumes [47]. To date, most studies of exercise performance have lasted only 6 weeks, but it seems likely that the benefits will be sustained.

EXACERBATIONS OF COPD

Not all COPD patients exacerbate, even those with more severe disease [48], but most do. The number of exacerbations is an important determinant of the subsequent deterioration of

TABLE 1 Modified summary of Global Initiative for Chronic Obstructive Lung Disease goals of therapy in chronic obstructive lung disease

Improve lung function[#]
Relieve symptoms
Prevent disease progression
Improve exercise tolerance
Improve health status
Prevent and treat complications
Prevent and treat exacerbations
Reduce mortality

[#]: not included in the original goals.

TABLE 2 Commonly used drugs prescribed in severe chronic obstructive pulmonary disease (COPD)

Medication	Route of administration	Dosage
Short acting β_2-agonists		
Salbutamol	Inhaler (MDI, DPI)	100–200 μg
	Nebuliser	2.5–5 mg
	Oral	8 mg
	Intravenous	3–20 μg·min^{-1}
Terbutaline	Inhaler (DPI)	500 μg
	Nebuliser	5–10 mg
	Subcutaneous	250–500 μg
Long-acting β_2-agonists		
Formoterol	Inhaler (MDI, DPI)	4.5–12 μg
Salmeterol	Inhaler (MDI, DPI)	25–50 μg
Short-acting anticholinergics		
Ipratropium bromide	Inhaler (MDI, DPI)	20–40 μg
	Nebuliser	0.5 mg
Long-acting anticholinergics		
Tiotropium	Inhaler (DPI)	18 μg
Combination short-acting β_2-agonist and anticholinergic		
Salbutamol/ipratropium	Inhaler (MDI)	100/20 μg
	Nebuliser	2.5/0.5 mg
Methylxanthines		
Theophlline	Oral	200–500 mg
Aminophylline	Oral	225–450 mg
	Intravenous	Variable
Inhaled corticosteroids		
Beclomethasone dipropionate	Inhaler (MDI, DPI)	100–1000 μg
Budesonide	Inhaler (MDI, DPI)	400–1600 μg
	Nebuliser	1–2 mg
Fluticasone propionate	Inhaler (MDI, DPI)	200–2000 μg
	Nebuliser	0.5–2 mg
Triamcinolone acetonide	Inhaler (MDI, DPI)	400–1200 μg
Mometasone furoate[#]	Inhaler (DPI)	200–800 μg
Ciclesonide[#]	Inhaler (DPI)	80–160 μg
Combination long-acting β_2-agonist and corticosteroid		
Formoterol/budesonide	Inhaler (DPI)	100/6–400/12 μg
Salmeterol/fluticasone	Inhaler (MDI, DPI)	100/50–500/50 μg
Oral corticosteroids		
Prednisolone	Oral	30–40 mg (in exacerbation)
Hydrocortisone	Intravenous	100–200 mg
Antioxidants		
N-acetylcysteine	Oral	600 mg
Mucolytics		
Carbocysteine	Oral	750 mg
Methyl cysteine hydrochloride	Oral	200 mg
Erdosteine	Oral	300 mg

MDI: metered dose inhaler; DPI: dry powder inhaler. [#]: no published data in COPD patients.

health status [49]. Persistent lower respiratory tract colonisation and a change in the bacterial strain within the airways explain why many exacerbations reoccur [50, 51]. Disappointingly, few studies have considered whether regular treatment with antibiotics can prevent these episodes, mainly because of understandable concerns about the development of antibiotic resistance. A large National Heart, Lung and Blood Institute-funded study is now underway to test the hypothesis that a low-dose macrolide antibiotic can reduce exacerbation frequency, while preliminary data from a UK study with erythromycin appears encouraging [52].

Regular treatment with a long-acting inhaled anticholinergic agent reduces exacerbation frequency [53], as do LABA [37]. Inhaled corticosteroids reduce the exacerbation rate in several placebo controlled trials [54], but the magnitude of the change

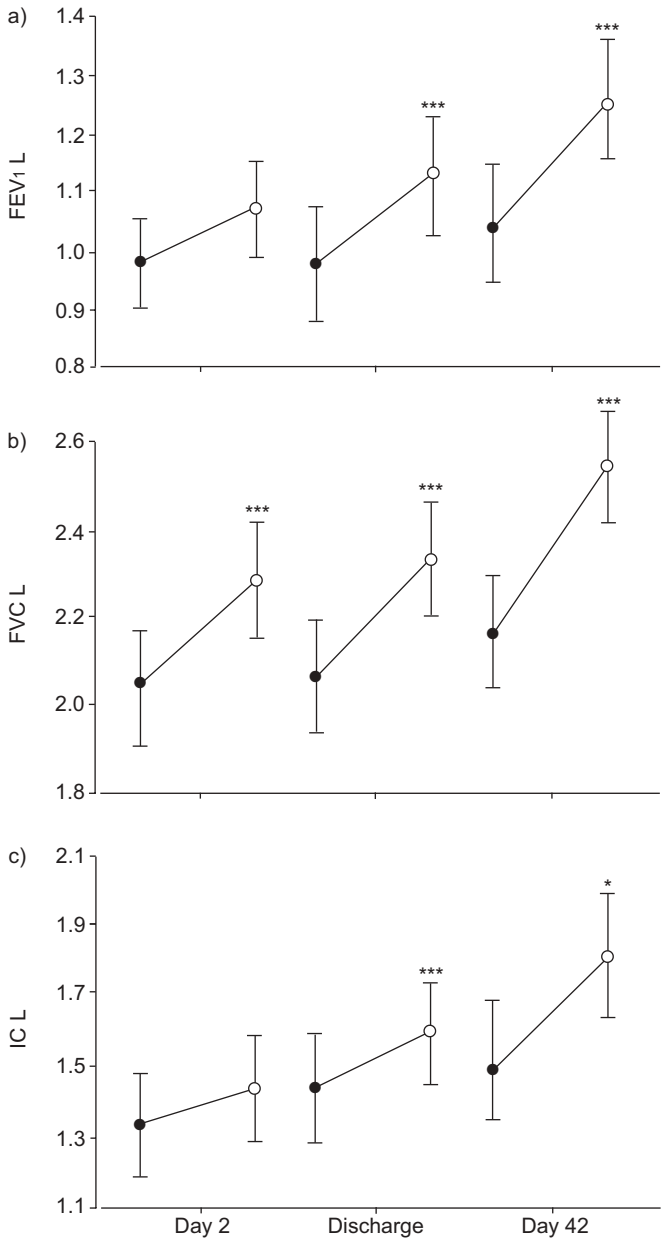

FIGURE 1. Changes in a) forced expiratory volume in one second (FEV_1), b) forced vital capacity (FVC) and c) inspiratory capacity (IC) and Borg dyspnoea score pre- (●) and post-bronchodilator (○; salbutamol and ipratropium) during and after an exacerbation. Note the reduction in dyspnoea initially when only the change in FVC was significant. Borg dyspnoea values pre- and post-bronchodilator, respectively, are as follows. Day 2: 3.6±0.4 and 3.0±0.4 ($p<0.05$); discharge: 2.8±0.2 and 2.5±0.25 ($p<0.05$); day 42: 2.8±0.3 and 2.15±0.3 ($p<0.05$). *: $p<0.05$; ***: $p<0.001$. Taken from data in [5].

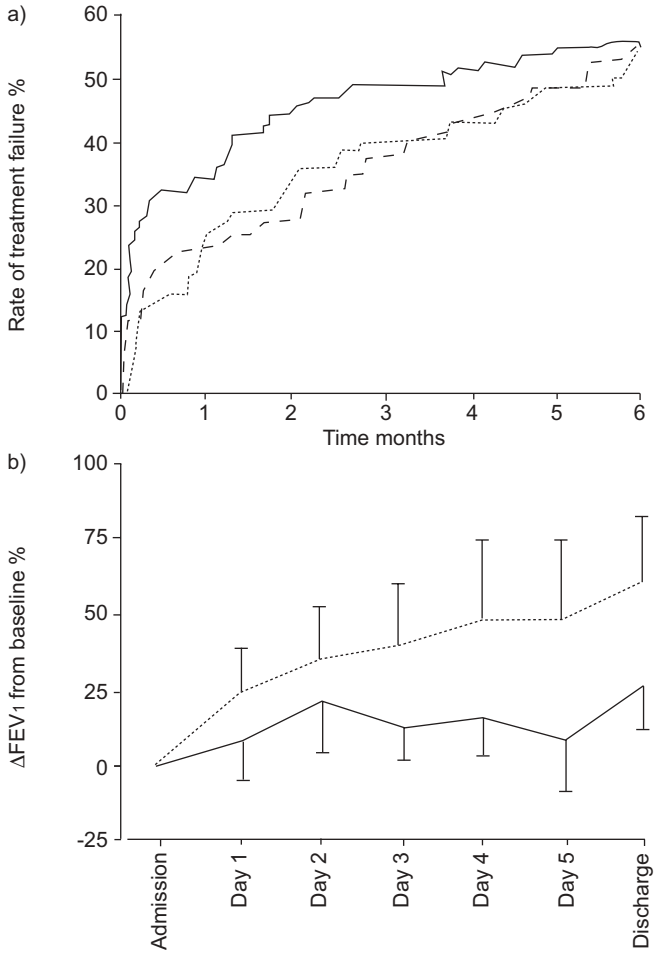

FIGURE 2. The likelihood of treatment failure after randomisation to systemic corticosteroids in the Veterans Administration Trial of Exacerbations of Chronic Obstructive Pulmonary Disease (COPD; a) and the recovery of lung function after treatment initiation for a COPD exacerbation in the UK study (b). Patients randomised to corticosteroids were less likely to exhibit early treatment failure, whatever the dose given, while recovery of forced expiratory volume in one second (FEV_1) was more rapid when oral prednisolone was prescribed. a) ———: treated with placebo; ·····: treated with glucocorticosteroids at 2 weeks; ------: treated with glucocorticosteroids at 8 weeks. b) ———: treated with placebo; ·····: treated with active corticosteroid. Taken from [16] and [17] with permission from the publishers.

and the method of expressing the data have been criticised [55]. Two studies with satisfactory methodology fail to show an effect of inhaled corticosteroids on exacerbation frequency, but did show that combining a LABA and a corticosteroid reduced the number of events over 1 yr [36, 56]. The TOwards a Revolution in COPD Health (TORCH) Study [37], again using a valid methodology to express the results, found a 25% reduction in exacerbations with a combination drug compared with a placebo, a difference that was significantly better than that due to the components [37]. There was no interaction with baseline FEV_1 in these results, suggesting that the benefits were seen in severe as well as milder disease. Both the LABA and combination treatment reduced the number of patients hospitalised and there was a strong trend in this direction with the anticholinergic treatment in the shorter 6-month trial studying this drug [53].

Antioxidant drugs, such as *N*-acetylcysteine, appear to decrease the number of exacerbations compared with placebo in a number of systematic reviews [57, 58], but when tested in a prospective clinical trial were only beneficial in patients who had not received an inhaled corticosteroid [59]. How these

effects translate to patients with more severe disease has not been studied.

HEALTH STATUS

Health status is severely impaired in advanced COPD, in part because of recurrent exacerbations, but also due to the limitations in exercise performance and the systemic impact of the disease as it worsens. Studies conducted over the last 5–6 yrs have reported health status as an outcome predominantly using the St George's Respiratory Questionnaire (SGRQ) total score. There are clear methodological difficulties here, as small but significant improvements are seen in the health status of patients randomised to placebo, possibly a result of participating in the clinical trial, but also reflecting the prolonged effect of prior exacerbations [60]. This was not seen when patients had their treatment intensified before randomisations [26, 36]. Interpreting a 4-yearly difference in health status, the minimum clinically important difference defined for the SGRQ [61] is difficult in the face of recall bias and differential study dropout, as seen in most of these COPD studies. Treatment modifies the time-course of the health status change and this is best seen in the 3-yr TORCH trial where patients who received placebo improved initially and then deteriorated over the remainder of the study, while those receiving the most effective treatment with the combination of drugs also showed the largest change in health status and remained better than at baseline, even at the end of the trial (fig. 3). This may be a more realistic way of assessing the effects of treatment over a longer period of time, at least until more effective treatment becomes available.

MORTALITY

COPD is still a major cause of death [2], although the cause of death varies with the stage of the disease. Patients with more severe disease die from COPD-related causes [40], although cardiovascular disease and cancer are still important factors [37]. Care is needed when attributing particular causes of death in a clinical trial [62]. COPD is often underestimated as a cause of death [63]. TORCH has been the only study thus far to report the effects of drugs on mortality, but failed to demonstrate conclusively a positive effect although the corrected p-value came very close to being significant ($p=0.052$) [37]. A *post hoc* analysis of the data suggested a positive effect of bronchodilator containing treatments, although this did not account for the interim adjustments in the primary analysis [64]. The size of the absolute benefit, a 2.6% reduction in all-cause mortality by 3 yrs, is comparable to that seen with cardiovascular treatments and, given that the study was eventually likely to be underpowered for the outcome it reported, it seems probable that a true-effect treatment on mortality exists that has not yet been firmly demonstrated.

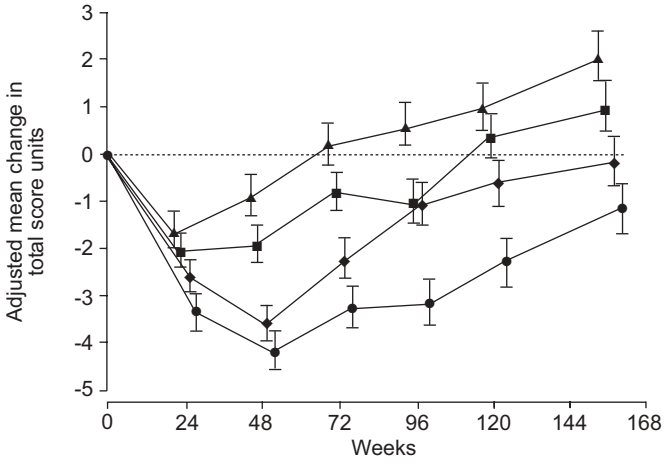

FIGURE 3. Time-course of change in total St George's Respiratory Questionnaire (SGRQ) score over the 3 yrs of the TOwards a Revolution in COPD Health (TORCH) Study [37]. After an initial improvement in the placebo-treated patients (▲) reflecting the loss of those with the worst initial health status, the SGRQ score declined. Long-acting β-agonist (salmeterol; ■) and inhaled corticosteroid (fluticasone; ♦) treatment delayed the onset of deterioration, but the greatest benefit was in the patients treated with combination therapy (●), where health status at 3 yrs was still better than at randomisation. Modified from [37] with permission from the publishers.

DRUGS FOR SYSTEMIC DISEASE

Impaired muscle function is likely to contribute to reduced exercise performance in COPD. Nutritional supplementation with creatine increases muscle bulk but does not improve exercise capacity [65], while testosterone was found to increase muscle strength and the ability to perform during resistance training in a relatively short-term study [66]. Increasing caloric intake is difficult in COPD as patients often reduce their daily food intake from other sources, but when calorie supplementation is achieved, it was found to have no benefit on exercise capacity in one randomised control trial [67]. However, there was a suggestion of benefit in patients who were better nourished and future studies may need to look at specific subgroups of patients to assess whether this therapy is worthwhile.

The high incidence of comorbidity in COPD, especially occult osteoporosis, irrespective of corticosteroid exposure [68], means that clinicians should be aware of other causes of disability apart from the lung disease. Recent data suggest that the osteoporosis tracks an increased degree of vascular stiffness [69]. This provides a mechanism to explain the apparent beneficial effect of receiving statin treatment, which was identified in large database studies of COPD patients [70–72]. This potentially important observation requires confirmation in prospective clinical trials.

ADVERSE EVENTS

All drug therapies have adverse events associated with them, although the treatments described in COPD are generally quite benign. Theophylline toxicity and particularly the occurrence of convulsions and ventricular tachycardia have led to a decline in the use of oral theophyllines. Concerns about the cardiovascular safety of LABA were laid to rest after the TORCH study [37] and, to date, tiotropium appears to be well tolerated and safe [73]. Inhaled corticosteroids can potentially increase the incidence of osteoporosis and cataracts, although this was not seen in the careful observations made during the 3 yr duration of the TORCH study; however, the TORCH study did identify the greater likelihood of patients randomised to inhaled corticosteroids having a clinically diagnosed pneumonia and this has been supported by a subsequent

database analysis [74]. This was a substantially less common occurrence than having a COPD exacerbation and did not translate into an increased mortality, hospitalisation rate or worsening health status, at least in patients receiving the β-agonist steroid combination in the TORCH study. However, it has emphasised the importance of identifying pneumonia in COPD patients and being aware of this possibility in those who receive inhaled corticosteroid therapy.

O_2 THERAPY

The physiological determinants of arterial O_2 tension and O_2 delivery to the tissues have been known since the 1970s and widely applied, especially in intensive care medicine. Less rigour has been used in evaluating how O_2 should be given to COPD patients, partly because of failure to regard O_2 as a drug. O_2 therapy in stable COPD can be used in the following three different ways.

To normalise arterial O_2 tension

This is the basis of domiciliary O_2 therapy and has been demonstrated in two landmark randomised studies in which active therapy and usual care were compared, to prolong life compared with patients who did not receive O_2 or in those who received 24- rather than 12-h treatment daily. In each study, participants had resting hypoxaemia, *i.e.* arterial O_2 tension <8.0 kPa, and O_2 treatment was found to increase these values to more normal values of $\sim$10 kPa in each study [75, 76]. The resulting reduction in all-cause mortality was accompanied by a fall or at least a failure in the progression of pulmonary hypertension and was well tolerated by the patient [75]. The only other large randomised clinical trial of O_2 treatment compared its effects in less hypoxaemic patient and failed to show any mortality benefit [77]. Similarly, there were no clear benefits in treating patients with isolated nocturnal hypoxaemia [78], while the increase in O_2 flow rate overnight originally recommended in the Nocturnal Oxygen Therapy Trial appears to be unnecessary [79]. These latter studies were relatively small and may have been underpowered to detect small differences between the treatment groups. This area is being re-visited in North America, where a large O_2 trial to determine whether O_2 therapy given to less hypoxaemic patient has some clinical benefit is in an advanced planning stage. As in other areas of COPD research, the practicality of studying a treatment that is already available to patients is proving to be a real challenge.

Reducing ventilatory drive during exercise

Increasing the inspired O_2 concentration reduces chemoreceptor input, even in normoxic subjects [80], and the resulting small reduction in minute ventilation is likely to be beneficial in COPD patients [81]. However, reducing lactate production in exercising muscle by improving O_2 delivery to the tissues is also important. Patients are considered for O_2 treatment during exercise in the presence of exercise-induced desaturation, but how well this tracks the other physiological changes is not completely clear. There is abundant data to show that administering O_2 during exercise, whether this is on a cycle ergometer, treadmill or during corridor walking, improves exercise performance and reduces the severity of breathlessness at the end of exercise [82–84]. This effect has been demonstrated when O_2 is given by face mask to patients at all stages of the disease [85]; there may be a dose–response relationship, although in practice, most portable O_2 delivery systems provide relatively low-flow O_2. One randomised crossover trial has shown that patients given ambulatory O_2 had improved quality of life in the 3-month treatment period [86]. However, more recently, there have been concerns that patients provided with ambulatory O_2 do not always use this, and this appeared to be true in a small randomised Canadian trial reported by LACASSE *et al.* [87]. More data about the actual use of O_2, as opposed to its potential in improving exercise capacity, will be important if this relatively expensive treatment is to be applied optimally.

Reducing the sensation of breathlessness

The relatively rapid reduction in ventilatory drive due to reduced chemoreceptor activity may explain the beneficial effects of O_2 in COPD patients who experience mechanical limitation to breathing during exercise or an acute exacerbation. Alternatively, a direct effect of cooling the upper airways [88] or the face [89] may be important and the relative contribution of these mechanisms in modifying breathlessness in COPD has not been studied. While there are plausible reasons to show that administering O_2, or at least cold air, in this way might be important, it has been much harder to demonstrate a worthwhile benefit, although early studies propose that giving O_2 before exercise or at the end of exercise would reduce breathlessness [90]. More recently, data from carefully controlled experiments have shown that O_2 increases inspiratory capacity more rapidly at the end of exercise than does room air breathing, but this does not translate into any significant change in the rate of improvement of breathlessness, irrespective of whether the O_2 is given through a mouthpiece or a face mask (fig. 4) [91]. Moreover, administering O_2 before exercise was found to be no better than air in preventing breathlessness occurring [92], and a carefully conducted 6-month trial of short-burst O_2 treatment in patients with severe COPD who were high consumers of healthcare showed no significant difference in either the health status of the patients or the healthcare utilisation when they had access to as-needed O_2 therapy [93]. Indeed, the number of cylinders used during the study [93] declined steadily, suggesting an early placebo effect. Although the lingering suspicion persists that short-burst O_2 treatment may help some individuals, it is hard to define who these patients might be and how they can best be identified. Assessing the clinical value of treatment in this setting is always difficult when the patients themselves are likely to spontaneously improve without treatment. At present, short-burst O_2 is not recommended and other better validated treatment approaches should be used in patients with severe disease.

COMBINING TREATMENTS

The intractable nature of COPD makes a combination of different treatment approaches desirable. This can be done at the pharmacological level where combinations of β-agonist and anticholinergics, either separately or in the same inhaler, have been used for many years and produce better bronchodilatation than either drug alone [94]. Data with longer acting agents is more limited and largely confined to short-term changes in FEV1. Thus, adding once-daily formoterol to tiotropium produced more bronchial dilatation during the

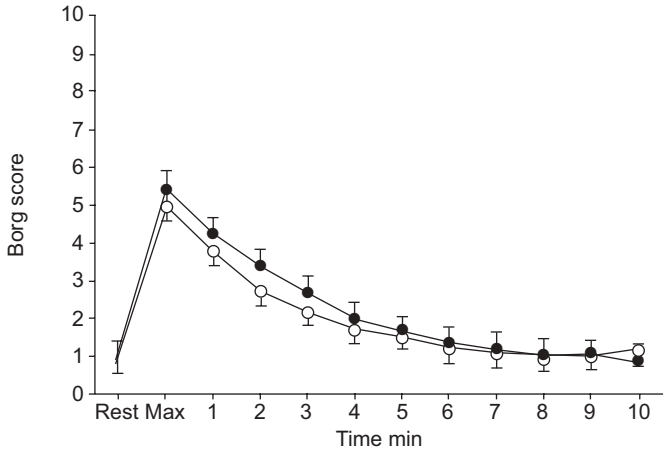

FIGURE 4. Recovery of Borg dyspnoea score in chronic obstructive pulmonary disease patients exercising to comparable symptom intensity and then receiving either medical air (●) or high-flow oxygen (○) *via* a non-rebreathing face mask. Oxygen did not change the rate of recovery of breathlessness. Reproduced from [91] with permission from the publisher.

day than either agent alone, but, as anticipated, the effect declined overnight [95]. One large, randomised, controlled clinical trial (the Canadian Optimal Therapy of COPD Trial) failed to demonstrate convincing bronchodilatation with a combination of tiotropium and salmeterol, but larger studies than this would be needed to assess this option treatment systematically [96]. As already noted, LABA and inhaled corticosteroids combined in single inhalers have multiple favourable clinical effects. The logical extension of this result was also studied in the OPTIMAL study, namely the combination of an anti-cholinergic drug with a steroid β-agonist combination inhaler. The primary outcome of this study was the number of exacerbations. It did not differ between any of the three treatment limbs, although the trial may have had insufficient power to demonstrate this using the pre-specified method of analysing exacerbations. However, patients receiving the combination therapy were significantly less likely to withdraw from the study, and had better lung function and health status than either bronchodilator-only regime. Further studies of this type will help to clarify the management of more severe COPD. Adding oral theophylline to other treatments can produce additional improvement in the FEV1 [97], and low-dose theophylline alone does appear to reduce exacerbation numbers [98], although comparison with other agents is needed to establish whether this is still true in more severe disease.

Recently, combinations of O_2 and bronchodilators have been studied in short-term comparisons. These show that the effects on exercise performance of these drugs is additive, with O_2 slowing the rate of increase of end-expiratory lung volume and bronchodilators increasing inspiratory capacity and so ''creating more space'' in which hyperinflation can occur [99]. These data have been confirmed using 6-min walking tests in patients with more severe COPD (fig. 5) [100], and suggests that O_2 during exercise may offer significant benefits that cannot be produced by pharmacological therapy alone.

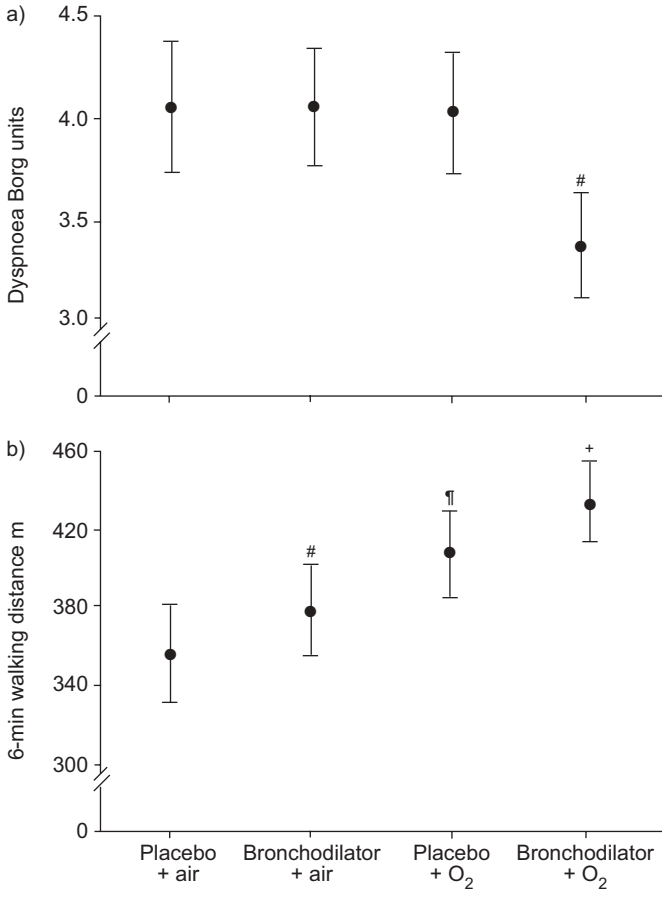

FIGURE 5. The effect of nebulised salbutamol + ipratropium and supplementary oxygen individually and in combination on a) the intensity of breathlessness and b) the 6-min walking distance. The 6-min walking distance was increased significantly by each treatment, while end-exercise dyspnoea was significantly less when bronchodilators and oxygen were combined. #: significantly different from air; ¶: different from air and bronchodilators; +: different from all other treatments. Reproduced from [100] with permission from the publisher.

CONCLUSIONS

Abundant evidence of the benefits of treatment in more severe chronic obstructive pulmonary disease is available. For most patients with a history of exacerbations, a long-acting inhaled bronchodilator, such as tiotropium, a combination of a long-acting β-agonist or an inhaled corticosteroid, will be needed and for many; all three agents represent the optimum treatment combination. Relying on a combination of short-acting bronchodilators and an inhaled corticosteroid confers a small but definite increased risk of pneumonia without the same treatment benefits, which include fewer hospitalisations and a potential for a better life-expectancy. The role of antioxidants and regular antibiotic prophylaxis is still controversial and neither can be recommended for routine use at present. For those with resting hypoxaemia, regular domiciliary oxygen treatment is mandatory. The evidence for ambulatory oxygen as a way of improving exercise performance is good, but more studies will need to identify the practical way in which this benefit can be realised, while short-burst oxygen treatment appears to rely more on a placebo effect than a physiological benefit. None of these treatment approaches

stand alone and, whether used to aid smoking cessation or combined with nonpharmacological treatment, such as pulmonary rehabilitation, they should form a part of an individualised management plan that is aimed at maximising the well-being of each chronic obstructive pulmonary disease patient with severe disease.

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