Caring for patients with advanced COPD: beyond the inhalers…

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Shareable abstract (@ERSpublications)
Patients with advanced COPD have many symptoms; optimising care goes beyond inhaler therapy and focuses on their individual needs including respiratory failure assessment, dyspnoea management, lung volume reduction and/or transplant and palliative care https://bit.ly/43Hp7wG

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Abstract

COPD affects millions of people worldwide. Patients with advanced COPD have a high symptom burden. Breathlessness, cough and fatigue are frequent daily symptoms. Guidelines often focus on pharmacological treatment, especially inhaler therapy, but other approaches in combination with medications offer symptomatic benefit.

In this review, we take a multidisciplinary approach with contributions from pulmonary physicians, cardiothoracic surgeons and a physiotherapist. The following areas are addressed: oxygen therapy and noninvasive ventilation (NIV), dyspnoea management, surgical and bronchoscopic options, lung transplantation and palliative care. Oxygen therapy prescribed within guidelines improves mortality in patients with COPD. NIV guidelines offer only low-certainty instruction on the use of this therapy on the basis of the limited available evidence. Dyspnoea management can take place through pulmonary rehabilitation. Specific criteria aid decisions on referral for lung volume reduction treatments through surgical or bronchoscopic approaches. Lung transplantation requires precise disease severity assessment to determine which patients have the most urgent need for lung transplantation and are likely to have the longest survival. The palliative approach runs in parallel with these other treatments, focusing on symptoms and aiming to improve the quality of life of patients and their families facing the problems associated with life-threatening illness. In combination with appropriate medication and an individual approach to symptom management, patients' experiences can be optimised.

Educational aims

- To understand the multidisciplinary approach to management of patients with advanced COPD.
- To recognise the parallel approaches to oxygen, NIV and dyspnoea management with consideration of more interventional options with lung volume reduction therapy or lung transplantation.
- To understand the high level of symptomatology present in advanced COPD and the relevance of palliative care alongside optimal medical management.

Introduction

There are an estimated 65 million people with moderate-to-severe COPD worldwide [1]. Patients with advanced COPD can be very symptomatic. Despite optimisation with medical treatments, patients continue to experience a variety of symptoms, with breathlessness, fatigue and cough, resulting in a loss of capability that is consistently reflected in synthesised studies of the qualitative data [2]. This is associated with an unrelenting psychosocial impact of the disease. Multimorbidity adds to the symptoms. Anxiety and depression are also highly prevalent. Breathlessness can lead to a limit in function that leads to isolation and loneliness.

The medical treatment and management of COPD has been well categorised in an incremental, stepwise manner in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, with additional therapies added at each stage of the disease [3]. Smoking cessation, vaccination and pulmonary

rehabilitation are first-line treatments and recommended for all. Indeed, smoking cessation is the most effective strategy for slowing down the progression of COPD, as well as increasing survival and reducing morbidity [4]. There are limitations to the treatment that we have to offer patients with COPD. From the TORCH study and many randomised controlled trials (RCTs), pharmacological therapy has been shown to have modest effects on airflow limitation and exacerbation rate but does not impact on survival [5]. Pulmonary rehabilitation and even transplant improve exercise capacity, exacerbation frequency and quality of life but not survival [6]. Apart from long-term oxygen therapy (LTOT) and surgery in a select few patients, survival is not altered [7].

In this article we aim to go beyond the pharmacological therapy and take a multidisciplinary approach to the patient with advanced COPD by addressing the areas of:

- Oxygen therapy and noninvasive ventilation (NIV)
- Dyspnoea management
- Lung volume reduction procedures
- Lung transplantation
- Palliative care

Oxygen therapy and NIV

Oxygen

The role of oxygen therapy has long been established in COPD and is supported by two landmark trials from over 40 years ago. The Nocturnal Oxygen Therapy Trial (NOTT) included 203 hypoxaemic COPD patients and showed that continuous oxygen therapy was superior to 12 h of nocturnal oxygen therapy with a mortality benefit at 1 year (11.9% mortality in the continuous group and 20.6% in the nocturnal oxygen group) [8]. The Medical Research Council (MRC) trial published a year later enrolled 87 COPD patients with COPD and severe hypoxaemia and carbon dioxide retention [9]. Subjects randomised to no supplemental oxygen had a mortality rate of 67%, while the study group on 2 $L \cdot min^{-1}$ for at least 15 h per day had a mortality rate of 45% over the 5 years of the study. On the basis of this convincing evidence, LTOT is prescribed for COPD patients with resting hypoxaemia; arterial oxygen tension (P_{aO_2}) <55 mmHg (7.3 kPa) or 59 mmHg (8 kPa) with evidence of right heart strain or polycythaemia (figure 1).

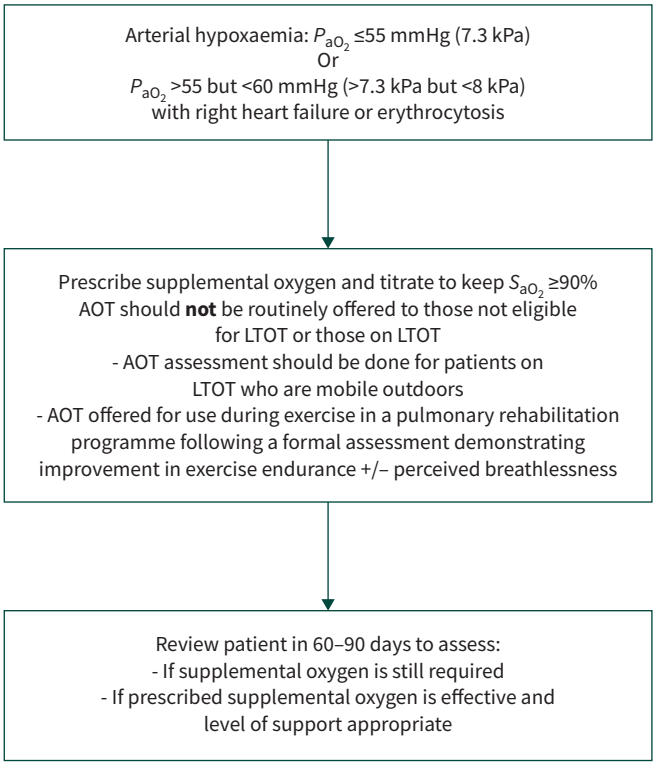

FIGURE 1 Prescription of supplemental oxygen for patients with COPD. P_{aO_2}: arterial oxygen tension; S_{aO_2}: arterial oxygen saturation; AOT: ambulatory oxygen therapy; LTOT: long-term oxygen therapy.

Some unanswered questions remain when it comes to prescribing oxygen outside of these strict parameters. The difference between evidence and practice was the motivation behind the Long-Term Oxygen Treatment Trial (LOTT) [10]. Subjects with moderate hypoxaemia (peripheral oxygen saturation (S_{pO_2}) 89–93%) and moderate exercise-induced desaturation S_{pO_2} <90% for >10 s and S_{pO_2} >80% for >5 min during the 6-min walk test were randomised to receive oxygen or no oxygen. A large cohort of 738 patients were enrolled and no differences were found between the oxygen and no oxygen groups in terms of time of death or first hospitalisation or the rates of hospitalisations or COPD exacerbations. There was also no difference in 6-min walk distance, lung function or health-related quality of life score (HRQL). This paper has been the subject of much discussion. Based on expert opinion, the evidence can be used not to instigate oxygen supplementation in patients who are not eager to pursue it [11] with an option to formally assess with a blinded exercise test while breathing either air or oxygen [12], although other interventions to target breathlessness should be the focus. Criticisms of the paper include selection bias and a lower duration of oxygen delivery time (13.6 h per day) compared with previous studies. Smaller studies have shown benefit from oxygen therapy in mildly hypoxaemic COPD patients in terms of quality of life, reduction in anxiety and depression scores, and 6-min walk distances [11].

Oxygen is sometimes considered as a palliative measure for the treatment of dyspnoea, but the assumption that oxygen can relieve dyspnoea is not based on fact and in the absence of hypoxaemia the use of oxygen to alleviate breathlessness is not supported by the literature. Campbell *et al.* [13] found no reduction in respiratory distress in subjects near death from respiratory failure. Addressing other approaches to dyspnoea is important in these patients.

NIV and high flow nasal oxygen

The long-term use of NIV is less clearly established. Noninvasive positive pressure ventilation administered by home ventilators is a bilevel positive airway pressure therapy.

On the basis that hypercapnia is known to be associated with increased mortality [14, 15], physiologically NIV would help reduce the impact of hyperinflation on respiratory muscle workload and ventilatory chemosensitivity to carbon dioxide would improve. In a study of 144 stable hypercapnic COPD patients, published in 2009, McEvoy *et al.* [16] found in favour of NIV plus LTOT compared with LTOT alone in terms of a survival benefit (28 months *versus* 20.5 months; mean inspiratory positive airway pressure (IPAP) was 13 cmH_2O, expiratory positive airway pressure (EPAP) 5 cmH_2O). In 2014, another RCT of 195 patients with COPD and stable chronic hypercapnia compared LTOT with long-term home NIV (LTH-NIV) but targeted carbon dioxide reduction (mean IPAP 22 cmH_2O, mean EPAP 5 cmH_2O used to decrease arterial carbon dioxide tension (P_{aCO_2}) by at least 20%) and showed a 1-year survival benefit (1-year mortality in the intervention group 12% *versus* 33% in the control group) [17]. Many studies followed and pooled analysis of 13 RCTs on the use of NIV in stable hypercapnic patients with COPD showed an overall minimal effect on mortality (RR 0.86) or hospitalisations (mean difference 1.26 fewer hospitalisations) [18–25].

NIV may improve exercise capacity and outcomes of pulmonary rehabilitation by resting fatigued muscles and improving mechanics and daytime gas exchange [20]. Seven RCTs evaluated HRQL and found that HRQL was higher with NIV [26]. Kohnlein *et al.* [17] found that HRQL was improved more with NIV plus LTOT than with LTOT alone.

Other trials investigated the use of LTH-NIV use after an episode of acute hypercapnic respiratory failure in patients with COPD. An initial smaller study showed no mortality benefit [27]. The RESCUE RCT included 201 COPD patients admitted with acute hypercapnic respiratory failure and prolonged hypercapnia with half randomised to NIV plus LTOT and the control group on LTOT. After 1 year there was no difference between the two groups in the primary outcome of time to readmission or death [28]. The HOT-HMV trial studied 116 COPD patients with persistent hypercapnia 2–4 weeks after a life-threatening episode of acute on chronic respiratory failure. This study found that NIV plus LTOT resulted in an increased time to readmission or death within 12 months (4.3 months *versus* 1.4 months) [29]. Data from a short-term trial focusing on physiological benefits, which was not an RCT, showed that delivery of higher levels of pressure support was associated with better compliance and a greater subjective benefit in chronically symptomatic patients [30]. Pooled data from five RCTs comparing higher levels of pressure support at 6 weeks compared to lower levels found no effect on HRQL [18].

Guidelines have been published by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) to aid clinical decision making in light of the data. The ERS guidelines on LTH-NIV for COPD offer conditional support for the use of NIV to improve health outcome by targeting a reduction in

carbon dioxide in COPD patients with persistent hypercapnic respiratory failure [18]. The recommendation is prefaced by a statement that the evidence base is weak. On the question of whether NIV should be used in stable patients with COPD, a conditional "yes" is offered by the ERS guidelines. Further support is suggested for use of NIV after a patient has presented with an episode of acute hypercapnic respiratory failure. These patients are known to have a high risk of repeat admission and may traditionally be the patients considered for home NIV. On the basis that home NIV is not associated with a reduction in mortality in the setting of acute hypercapnic respiratory failure but is associated with some reduction in exacerbations, time to readmission and some parameters of dyspnoea and quality of life a low evidence recommendation in favour of NIV in this setting is made.

The suggestion that we should treat to normalise or to reduce P_{aCO_2} is a conditional, very low-level evidence suggestion. High-intensity NIV with IPAP up to 30 cmH_2O with a high back-up rate theoretically should correct nocturnal alveolar hypoventilation. Despite the low level of evidence, the reason given for the positive recommendation states the low risk of harm. Fixed pressure support is suggested as the first-choice mode for home NIV for COPD patients as opposed to volume-targeted NIV without any current established benefit from auto-titrating pressure modes [18].

The ATS guidelines on LTH-NIV in chronic stable hypercapnic COPD patients were published 1 year after the ERS guidelines and were largely based on the same evidence [31]. The guidelines reflected similar themes to the ERS document stating "conditional" and "very low" to "moderate" level certainty. The two main differences across the Atlantic were: 1) the suggestion that NIV would not be started during an admission with hypercapnic respiratory failure but deferred until 2–4 weeks after; and 2) obstructive sleep apnoea (OSA) screening was suggested prior to the NIV initiation. The ATS document suggests that the increased incidence of obesity in the USA may mean that OSA is a more frequent comorbidity.

The question of cost-effectiveness of LTH-NIV needs to be considered. A study with a Markov model-based cost-utility analysis from the UK National Health Service investigated cost-effectiveness for two advanced COPD patient cohorts: those commenced on NIV who were stable without a recent admission and a group commenced on domiciliary NIV post-hospitalisation for an exacerbation [32]. Based on calculations, the authors concluded that NIV appears to be cost-effective when started immediately after or within 4–6 weeks of a hospital admission in which NIV was required (incremental cost-effectiveness ratio (ICER) GBP 11 318 per quality-adjusted life-year (QALY) gained) but uncertainty remained around the cost-effectiveness of domiciliary NIV (ICER GBP 27 380 per QALY, only 4% likely to be cost-effective at the GBP 20 000 per QALY threshold).

The evidence suggests that specific patients with advanced COPD and hypercapnic respiratory failure may benefit from LTH-NIV; however, individual patient characteristics and preferences, local infrastructure, cost and expertise need to be taken into account. Comorbidities such as malignancy, heart failure and OSA are exclusion criteria in most RCTs and the impact of age has not been evaluated. Considering the option of LTH-NIV should be reviewed in the context of the overall picture of the other treatment options in this patient group.

FRAT *et al.* [33] showed that high flow nasal oxygen (HFNO) was non-inferior to standard oxygen therapy or NIV in preventing intubation with non-hypercapnic acute hypoxic respiratory failure. The use of HFNO is increasing in admitted COPD patients with acute exacerbations and could help with secretion removal and reduce the work of breathing especially in patients who do not require NIV management as part of their treatment, but have severe hypoxaemic respiratory failure [34]. There are a number of proposed benefits for this specific subgroup of patients, who have a significant degree of mucus burden but do not have severe acidotic respiratory failure. The humidification of air may help remove secretion burden and reduce airway inflammation. It also gives additional intrinsic positive end-expiratory pressure (PEEPi) and so may reduce the work of breathing [35]. The high-flow oxygen reduces dead space and this has been shown to reduce P_{aCO_2} [36]. RCTs are needed to clarify the real efficacy of HFNO and the best target population during COPD exacerbation.

Dyspnoea management

Dyspnoea is a cardinal symptom of COPD and is subjectively described as a discomfort of breathing. Its severity increases as the underlying disease progresses and can lead to significant limitations and disability as the body becomes more deconditioned [37]. It is believed that dyspnoea occurs from the disruption of the normal relationship between the inspiratory neural drive to breathe and the dynamic response of the respiratory system [38]. The respiratory system is designed to maintain homeostasis in terms of gas exchange and normalising pH. If the expected airflow into the lungs is not achieved, or if the displacement

of the lungs and chest wall is inadequate, then an imbalance occurs and can result in the development of dyspnoea [39].

There are different action plans for acute breathlessness and chronic breathlessness. In acute breathlessness the symptom is triggered. The patient may start to feel anxious or overwhelmed and experience physical changes such as muscle tightness and increased respiratory rate which in turn impact on the sensation of breathlessness. Using reliever inhalers, adopting positions-of-ease and doing breathing control and airway clearance exercises are the initial steps. Chronic breathlessness is breathlessness which persists despite optimal treatment of the underlying disease and its severity is increased with increasing airflow limitation [40]. Self-management techniques and lifestyle changes can be very helpful in this instance. Overall, the promotion of regular physical activity, particularly the participation in pulmonary rehabilitation programmes has proven efficacy in reducing dyspnoea and is recommended in international guidelines for patients with COPD and persistent dyspnoea [6].

Finding the right position-of-ease to relieve dyspnoea, reduce effort on accessory muscles and help with sputum clearance is best practised when the patient is stable. Commonly, the forward lean position (resting forearms on the thighs or a table) is most helpful for those with an obstructive pattern (figure 2). Those with restrictive patterns can respond best to sitting upright in a supported high-backed chair. A walking aid may help decrease the work of breathing by bracing the arms on the aid and adopting a forward-lean position which stabilises the ribcage, allowing the accessory muscles to better engage in respiration (figure 3). It may also be a consideration in the presence of portable oxygen.

Breathing techniques can help the patient feel confident that they have the knowledge and ability to tackle unexpected episodes of breathlessness. Controlled breathing is normal tidal breathing using the lower chest on inspiration while relaxing the upper chest, and then relaxing the stomach on expiration (rise, relax, rest). It can be used to promote slow regular breaths, focusing the mind on positive thoughts: “I have experienced this before; I know it will subside, I need to adopt my position-of-ease, and I will be okay”.

For acute dyspnoea, techniques used start with pursed lip breathing which can decrease respiratory rate, increase vital capacity, and improve gas exchange. The patient can then proceed on to controlled breathing to normalise their respiratory rate. For exertional dyspnoea, the “blow-as-you-go” technique helps make tasks easier: it uses the pursed lip breathing technique and times expiration with effort of the task. Paced breathing can be useful for when climbing stairs or walking (see www.blf.org.uk).

Dyspnoea can be provoked by bouts of coughing and retained sputum. The active cycle of breathing technique (ABCT) is a set of exercises which loosen secretions and helps with expectoration by using a forced expiration “huff”, which is less fatiguing than coughing. A breath is taken in, and with an open mouth and glottis the air is then squeezed out using the chest wall and abdominal muscles [41].

FIGURE 2 Position of ease: the forward lean position (resting forearms on the thighs or a table) is most helpful for those with an obstructive pattern.

FIGURE 3 Position of ease in exercise: bracing the arms on a walking aid or handlebars, adopting a forward lean position stabilises the ribcage, allowing the accessory muscles to better engage in respiration.

Neuromuscular transcutaneous electrical stimulation (NMES) has been linked to increased muscle strength, functional capacity and health status in COPD patients, and unlike physical exercise, does not evoke dyspnoea [42]. Vieira *et al.* [43] found that NMES in COPD patients significantly increased 6-min walk test distances by 87 m ($p<0.01$) and has potential to be considered as an adjunctive technique to exercise. However, the commitment on behalf of the participants and staff was significant, requiring sessions of 60 min, twice daily, five times per week for 8 weeks.

Another non-pharmacological strategy recommended by the ATS is the use of a hand-held fan to help modulate the perception of breathlessness and the person's response to it. The fan is thought to stimulate the upper airway receptors or trigeminal skin receptors. The draught of cool air directed 6 inches from the face, in the three clinical trials reviewed by Luckett *et al.* [44] resulted in a perceived benefit by 72% of participants in terms of a quicker recovery from breathlessness.

Reduced exercise tolerance in patients with COPD is multifactorial. Altered skeletal muscle function, strength and endurance are affected by systemic factors such as inflammation, medication and inactivity, and changes in protein expression can result in a reduction of muscle mass, depressing the contractile function of skeletal muscles [45]. Progressive dynamic hyperinflation and subsequent dyspnoea also play a significant role in reduced exercise capacity. To avoid exertional dyspnoea, patients often avoid exercise, leading to a "dyspnoea spiral" [46]. There is a known link between oxygen supply and muscle contraction; weaker muscles need more oxygen to work. Thus, exercising regularly can make muscles stronger so that less oxygen is required to do the same amount of activity.

Pulmonary rehabilitation is a 6–8-week structured exercise programme which establishes an environment that normalises the feeling of being short of breath and sees it as a positive reaction to keeping the body fit and strong [47]. The benefits include improved dyspnoea, health status and exercise in stable patients and it also reduces symptoms of anxiety and depression [6]. The modified BORG Dyspnoea Scale is an outcome measure scale which uses specific descriptors of dyspnoea and has been validated as a clinical tool to prescribe workload during muscle training and physical exercise [48]. During pulmonary rehabilitation, this scale helps to judge intensity at an individual level and exercises may be progressed or modified based on symptoms. Interval training at high intensities allows patients to tolerate higher training load with less dyspnoea and leg fatigue as it is interspersed with periods of active recovery or rest. Resistance training provides greater increases in muscle mass and strength and is less strenuous on the breathing system than endurance training, which can be a more positive feature when looking to improve overall activity. All of these factors are combined to deliver an individualised, group-based progressive exercise class with a structured multidisciplinary education programme [49].

The multidisciplinary team (MDT) focus on self-management education covering topics of breathlessness management, nutrition (to make the body stronger, help it fight infections and maintain a healthy weight),

energy conservation (by prioritising what needs to be done, pacing techniques and using the BORG scale, planning to do tasks and timing them around when your energy levels are high, linking breathing and swallowing of food and saliva) and lifestyle behaviour changes such as smoking cessation, healthier eating and regular physical activity.

Lung volume reduction procedures

Lung volume reduction (LVR) is a treatment option for patients with end-stage COPD whose main complaint is dyspnoea. This encompasses endobronchial placement of valves (EBV-LVR) or minimally invasive keyhole surgery, such as robot-assisted LVR surgery (RATS-LVRS) or video-assisted LVRS (VATS-LVRS). Surgical LVR is an effective, established treatment for selected patients with severe emphysema and has been shown to provide improvements in health status and lung function outcomes [50–52].

LVRS was initially introduced in the 1930s and aims to remove diseased, hyperinflated lung; enhancing the remaining, more functional lung to improve exercise tolerance and breathlessness at rest [53]. Due to high morbidity, it fell out of routine use until the National Emphysema Treatment Trial (NETT) demonstrated the clinical benefit of LVRS in selected subgroups [7]. They concluded that patients with a low forced expiratory volume in 1 s (FEV_1) of <20%, homogenous emphysema or a very low transfer factor for carbon monoxide (T_{LCO}) of <20% were at increased risk for morbidity post-surgery [54]. More modern surgical techniques, such as VATS instead of midline sternotomies, have led to a decrease in the mortality associated with LVRS [55]. The mortality rate of 5.5% in NETT trial from 2003 is overstated compared with 2021 figures (2.2% in the post-operative period) [56]. Robotic LVRS has recently been introduced into practice as an alternative to VATS-LVRS, using real-time Firefly perfusion to identify perfusion defects [57]. Both VATS-LVRS and RATS-LVRS involve the resection of hypo-perfused lung using staples and are typically carried out unilaterally in a specialised thoracic centre. This directly reduces residual volumes, providing symptomatic relief for this dyspnoeic cohort.

Bronchoscopic interventions for the treatment of COPD, including EBV-LVR, have been developed to address the invasive and irreversible nature of surgical LVR. These one-way valves reduce lung hyperinflation by lobar collapse of the targeted site [58] and can be carried out under general anaesthesia or sedation. Other LVR interventions that are mentioned in literature include endobronchial coils, thermal vapour ablation (TVA), targeted lung denervation (TLD) and airway bypass stent (ABS) [12]. Improvement in quality-of-life metrics post-LVR has been established, with a mean reduction in St George's Respiratory Questionnaire of 19.61 units in an Irish cohort comparing EBV, RATS-LVRS and VATS-LVRS [59]. Gompelmann *et al.* [60] have reported on a long-term follow-up of EBV-LVR patients with lobar atelectasis who had a significant improvement in overall survival with a 5-year survival rate of 65.3% as compared to patients without lobar atelectasis, *i.e.* without a LVR effect, of 43.9% at 5 years. There was improvement in baseline pulmonary tests for patients with lobar collapse in this cohort [60].

LVR is a complex procedure, balancing medical optimisation, fitness to undergo a procedure and the patient's motivation to proceed involves a stringent screening process. Optimisation of overlapping phenotypes (small airways disease, malacia, bronchitis, bronchiectasis, sleep apnoea, pulmonary hypertension) and comorbidities (reflux, ischaemic heart disease) should be considered. As a general starting point, any patient with severe emphysema (defined as patient achieving an $FEV_1 \leqslant 50\%$; GOLD Stage 3 or 4 [3]) who remains breathless on optimal pharmacological therapy and who has completed a course of pulmonary rehabilitation is referred for further assessment. The selection criteria for LVR are multifactorial, encompassing clinical factors, degree of hyperinflation, patient motivation and patient goals of care. The referral criteria are summarised in table 1.

LVR aims to reduce hyperinflation; this relieves dyspnoea on exertion, and at rest. A StratX report (based on a high-resolution, non-contrast computed tomography (CT) thorax) gives a report on fissure completeness and emphysema index (a measure of emphysematous destruction of lung tissue). A bronchoscopy is carried out routinely and a Pulmonx Chartis assessment is carried out to assess for inter-lobar collateral ventilation. If this is found, EBV-LVR will be unsuitable for this patient and RATS-LVRS or VATS-LVRS may be offered. A ventilation/perfusion scan identifies a target perfusion deficit. EBV-LVR patients must meet the above outlined criteria; however, as it is a minimally invasive procedure there is a reduced operability threshold. Therefore, patients who undergo EBV-LVR can have increased comorbidity which may render them unsuitable for VATS-LVRS or RATS-LVRS.

In UK general practice, it has been estimated that 8.1% of patients with COPD meet eligibility criteria to be assessed for a possible LVR procedure [61]. The complexity of this patient cohort's care necessitates input from a MDT. COPD, or hyperinflation, MDTs have been set up in different centres in the UK. They

TABLE 1 The selection criteria for lung volume reduction

Referral criteria	Exclusion criteria
COPD/emphysema GOLD stage 3 or 4	Severe bronchiectasis +/− tracheobronchomalacia
FEV_1 <50%	Smoker
TLC >100%	Severe pulmonary artery hypertension as defined (>55 mmHg)
RV >150% (due to variation in measuring volumes using helium or body box)	Moderate pulmonary artery hypertension (41–55 mmHg with right ventricular dysfunction)
Smoking cessation for a period >3 months	Significant cardiac disease
Enrolment into a pulmonary rehabilitation programme (current or in the preceding 12 months)	Severe comorbid illness or malignancy
T_{LCO} >20%	Clinically significant bronchiectasis or fibrosis

GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume; T_{LCO}: transfer factor of the lung for carbon monoxide.

commonly include a respiratory consultant, thoracic surgeon, interventional bronchoscopist, clinical nurse specialist, physiotherapist, palliative care input and consultant radiologists [53].

Transplant in COPD

COPD remains one of the most common indications for lung transplantation worldwide. However, not everyone with severe COPD will derive a benefit from lung transplant and challenges remain in choosing the right candidates. The trajectory of the illness in patients with severe COPD is highly variable despite low lung function. Focusing on potential quality of life benefits post-transplant become important areas of discussion.

Lung transplantation can be a lifesaving treatment option for patients with severe lung disease, which is refractory to conventional treatments. However, there is a significant disparity between the number of donor organs available and the number of potential recipients. It is generally recommended to consider transplantation when the patient is symptomatic during daily living activities (New York Heart Association (NYHA) class III or IV) and survival is expected to be limited to 2–3 years, which represents the upper end of the usual waiting time [62]. The chance of surviving the waiting period will depend on the waiting time, the underlying disease and the existing system for allocation of donor organs [63].

It is important to control and optimise available therapies, including LVRS and pulmonary rehabilitation, but also to weigh the risks and benefits of lung transplantation to each individual patient prior to a lung transplant referral. Other pre-existing conditions may affect patients' overall outcome and the long-term survival of the graft involves regular hospital reviews and surveillance bronchoscopies as well as taking a complex medicine regimen. Data from the International Society for Heart and Lung Transplantation (ISHLT) registry show a median survival of 6 years for patients who undergo lung transplantation for COPD [64]. The long-term success of lung transplant for the patient can often be reduced by opportunistic infection and rejection issues.

The ISHLT have published guidelines to aid referring teams on choosing the most appropriate patients for referral. It is important to define disease severity as precisely as possible in order to determine which patients have the most urgent need for lung transplantation and are likely to have the longest survival after transplantation.

Guidelines for timing a referral for a transplant assessment for patients with COPD and emphysema due to alpha-1 antitrypsin deficiency include the following:

- Progressive disease despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy
- Patient is not a candidate for surgical or endoscopic LVRS
- BODE (body mass index, airflow obstruction, dyspnoea, exercise capacity) index 5 to 6
- Post-bronchodilator FEV_1 20–25% of predicted
- Resting hypoxaemia, defined as P_{aO_2} <60 mmHg (8 kPa)
- Hypercapnia, defined as P_{aCO_2} >50 mmHg (6.6 kPa)
- Increase in BODE index score >1 over past 24 months and pulmonary artery to aorta diameter >1 on CT scan
- While T_{LCO} has not been shown to be an independent predictor of mortality in COPD, a low T_{LCO} has been associated with increased COPD symptoms, reduced exercise performance, and severe exacerbation risk, and thus, also may prompt consideration of referral [62, 65]

Following an initial review at the transplant referral clinic, the transplant physician may decide that a formal lung transplant assessment is appropriate, if the disease is severe enough and if there is an absence of other end-organ dysfunction or significant comorbidities (table 2). The lung transplant assessment process involves a series of investigations focusing primarily on understanding the vascular disease and potential malignancy profile of the candidate that can increase with age. Following an assessment, candidates are discussed at a lung transplant MDT meeting to discuss appropriateness of listing for lung transplant.

The following are suggested criteria for placing a patient with COPD on the transplant list (presence of one criterion is sufficient) [62]:

- BODE index $\geqslant 7$
- FEV_1 <15 to 20% of predicted
- Three or more severe exacerbations (hospitalisations) in the preceding year
- One severe exacerbation with acute hypercapnic respiratory failure
- Moderate-to-severe pulmonary hypertension

The 2022 ISHLT Adult Lung Transplant Report has recently published its findings on recipients who received a lung transplant for COPD over time. Lung transplant recipients transplanted for COPD are now older and more likely to be hospitalised or on mechanical ventilation with more comorbidities pre-transplant than previously. Patients seem also in certain age groups to have better survival with a double lung transplant for COPD than a single lung transplant and the report showed that 5-year survival conditioned at 1 year showed lower survival for single *versus* double lung transplant recipients in the age groups 40–59 years and >60 years [66].

Many challenges remain with appropriate lung transplant recipient selection for patients with COPD. All possible modifiable barriers should be optimised prior to lung transplantation to ensure the most effective long-term outcome. Prognostic models to predict the appropriate timing for referral are unpredictable even with patients with advanced disease and a careful benefit *versus* risk assessment is required to see who will derive benefit and improve their quality of life.

Palliative care in COPD

Patients with COPD have a high level of symptomatology daily. Those who care for patients with this condition often focus on the “acute” of the acute-on-chronic breathlessness leaving the “chronic” untreated. Palliative care is defined as an approach that improves the quality of life of patients and their families, in the face of a life-threatening illness. It is an approach focused on the prevention and relief of suffering. It puts the person before the disease, affirms life and regards death as a normal process [67].

It can be difficult to know when to consider a palliative approach, but guidelines suggest it should begin at the time of diagnosis of a life-limiting illness [6, 68]. Despite these recommendations, there is low uptake of palliative care services for COPD patients within primary care. A large UK cohort study showed that only 16.7% of deceased COPD patients who did not have an accompanying cancer diagnosis received palliative care services compared with 56.5% of deceased patients with COPD and lung cancer [69]. In the USA, insurers do not support coverage of this service unless the physician certifies that the patient will die within 6 months if the disease to take its usual course [70]. This can be challenging as COPD has an unpredictable course, punctuated by exacerbations and often without a distinct terminal phase. Predicting the terminal phase is difficult [71] and physicians’ ability to assess this in their patients is limited.

The respiratory triad of symptoms are those of breathlessness, fatigue and cough. Dyspnoea is defined as a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. Chronic breathlessness in advanced disease results from a number of pathophysiological processes, such as cachexia, deconditioning and airway narrowing.

The multidisciplinary approach addressing this complex symptom is addressed in the dyspnoea management section. The pharmacological approaches to managing dyspnoea come from three main drug classes: opioids, benzodiazepines and antidepressants.

Morphine has the largest evidence base though this is not substantial. A helpful practical paper in *Breathe* suggests starting on the lowest possible dose, increasing when necessary to 20 mg daily modified-release form and titrate up, if needed to a maximum of 30 mg daily, treating adverse effects actively [67]. Most patients in clinical trials have required no more than 30 mg per day, but it should be noted that two thirds of patients had stopped morphine at 3 months because of adverse effects (constipation, dysphoria, myoclonus, nausea and sedation) or lack of response.

TABLE 2 Risk factors for lung transplantation

Absolute contraindications Candidates with these conditions are considered too high risk to achieve successful outcomes post-lung transplantation	1) Lack of patient willingness for transplant 2) Malignancy with high risk of recurrence or death related to cancer 3) Glomerular filtration rate <40 mL·min^{-1} per 1.73 m^2 unless being considered for multi-organ transplant 4) Acute coronary syndrome or myocardial infarction within 30 days (excluding demand ischaemia) 5) Stroke within 30 days 6) Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant 7) Acute liver failure 8) Acute renal failure with rising creatinine or on dialysis and low likelihood of recovery 9) Septic shock 10) Active extrapulmonary or disseminated infection 11) Active tuberculosis infection 12) HIV infection with detectable viral load 13) Limited functional status (*e.g.* non-ambulatory) with poor potential for post-transplant rehabilitation 14) Progressive cognitive impairment 15) Repeated episodes of non-adherence without evidence of improvement (note: for paediatric patients this is not an absolute contraindication and ongoing assessment of non-adherence should occur as they progress through different developmental stages) 16) Active substance use or dependence including current tobacco use, vaping, marijuana smoking, or *i.v.* drug use 17) Other severe uncontrolled medical condition expected to limit survival after transplant
Risk factors with high or substantially increased risk	1) Age >70 years 2) Severe coronary artery disease that requires coronary artery bypass grafting at transplant 3) Reduced left ventricular ejection fraction <40% 4) Significant cerebrovascular disease 5) Severe oesophageal dysmotility 6) Untreatable haematological disorders including bleeding diathesis, thrombophilia, or severe bone marrow dysfunction 7) BMI >35 kg·m^{-2} 8) BMI <16 kg·m^{-2} 9) Limited functional status with potential for post-transplant rehabilitation 10) Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence without sufficient support systems 11) Unreliable support system or caregiving plan 12) Lack of understanding of disease and/or transplant despite teaching 13) *Mycobacterium abscessus* infection 14) *Lomentospora prolificans* infection 15) *Burkholderia cenocepacia* or *Burkholderia gladioli* infection 16) Hepatitis B or C infection with detectable viral load and liver fibrosis 17) Chest wall or spinal deformity expected to cause restriction after transplant 18) Extracorporeal life support 19) Retransplant
Risk factors Risk factors with unfavourable implications for short- and/or long-term outcomes after lung transplant While acceptable for lung transplant programmes to consider patients with these risk factors, multiple risk factors together may increase risk for adverse post-lung transplant outcomes	1) Age 65–70 years 2) Glomerular filtration rate 40–60 mL·min^{-1} per 1.73 m^2 3) Mild-to-moderate coronary artery disease 4) Severe coronary artery disease that can be revascularised *via* percutaneous coronary intervention prior to transplant 5) Patients with prior coronary artery bypass grafting 6) Reduced left ventricular ejection fraction 40–50% 7) Peripheral vascular disease 8) Connective tissue diseases (scleroderma, lupus, inflammatory myopathies) 9) Severe gastro-oesophageal reflux disease 10) Oesophageal dysmotility 11) Thrombocytopenia, leukopenia, or anaemia with high likelihood of persistence after transplant

Continued

TABLE 2 Continued

	12) Osteoporosis 13) BMI 30–34.9 kg·m^{-2} 14) BMI 16–17 kg·m^{-2} 15) Frailty 16) Hypoalbuminaemia 17) Diabetes that is poorly controlled 18) Edible marijuana use 19) *Scedosporium apiospermum* infection 20) HIV infection with undetectable viral load 21) Previous thoracic surgery 22) Prior pleurodesis 23) Mechanical ventilation 24) Retransplant >1 year for obstructive CLAD

BMI: body mass index; CLAD: chronic lung allograft dysfunction. Reproduced and modified from [65].

A recent study of the effect of morphine on breathlessness and exercise endurance in advanced COPD saw a randomised crossover trial investigate the acute effect of immediate release oral morphine *versus* placebo on physiological and perceptual responses during cardiopulmonary exercise test (CPET) in 20 adults with advanced COPD and chronic breathlessness syndrome [72]. In the morphine group breathlessness was reduced by 1.2 BORG units with exercise endurance time increased by 2.5 min. Breathing frequency during exercise was decreased by 2 breaths per min. CPET could be considered to separate responders from non-responders. A further trial of 111 participants investigated outcomes after 4 weeks of 10 mg sustained release morphine twice daily *versus* placebo [73]. The COPD Assessment Test score was 2.18 points lower in the morphine group and P_{aCO_2} was 1.19 mmHg higher. Breathlessness, however, remained unchanged but "worst breathlessness" improved in participants with mMRC grades 3 to 4. Five participants in the morphine group withdrew compared with one in the placebo group.

There is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD [74]. Benzodiazepines caused more drowsiness as an adverse effect compared with placebo, but less compared with morphine. Benzodiazepines may be considered as a second- or third-line treatment, when opioids and non-pharmacological measures have failed to control breathlessness.

Currently, there is insufficient evidence to support the routine use of antidepressants for chronic breathlessness in advanced disease [75, 76]. Mirtazapine is a promising candidate to pursue, with a RCT underway to determine its efficacy and safety in this setting [77].

Fatigue is a highly prevalent symptom in advanced respiratory disease and often overlooked. This is not simply tiredness but "incorporates total body feelings ranging from tiredness to exhaustion, creating an overall body condition which is unrelenting and alters the person's ability to function" [67]. Characteristically it is not improved by sleep or rest. There is some overlap with the dyspnoea treatments with exercise, cognitive behavioural therapy, pacing and prioritising being key approaches. Pulmonary rehabilitation reduces fatigue in COPD [78].

Cough can be a very distressing symptom, and a precipitator and exacerbator of breathlessness, anxiety and poor sleep in both the sufferer and those closest to them. Non-pharmacological interventions based on speech and language therapy have been used in chronic (idiopathic) cough with some success [67]. Drug therapy is imperfect: gabapentin, a central modulator of cough generation, is used but there is no guidance for its use in advanced respiratory diseases. Further information is outstanding on the use of gefapixant, a P2X3 receptor antagonist proven to have some benefit in refractory chronic cough and unexplained chronic cough [79]. This medication has not yet been licensed for use in the setting investigated and has not yet been investigated in cough associated with COPD. Taking 10 mg of oral modified release morphine has been shown to cause a statistically significant 40% reduction in cough scores in chronic cough compared with placebo but has not been tested for this symptom in COPD [80].

In terms of palliation, the holistic approach includes addressing comorbidities which may include anxiety (intrinsically linked with breathlessness), depression, nutritional deficits and inadequate sleep. Other important issues in community care include caring for the carers and optimising general health with

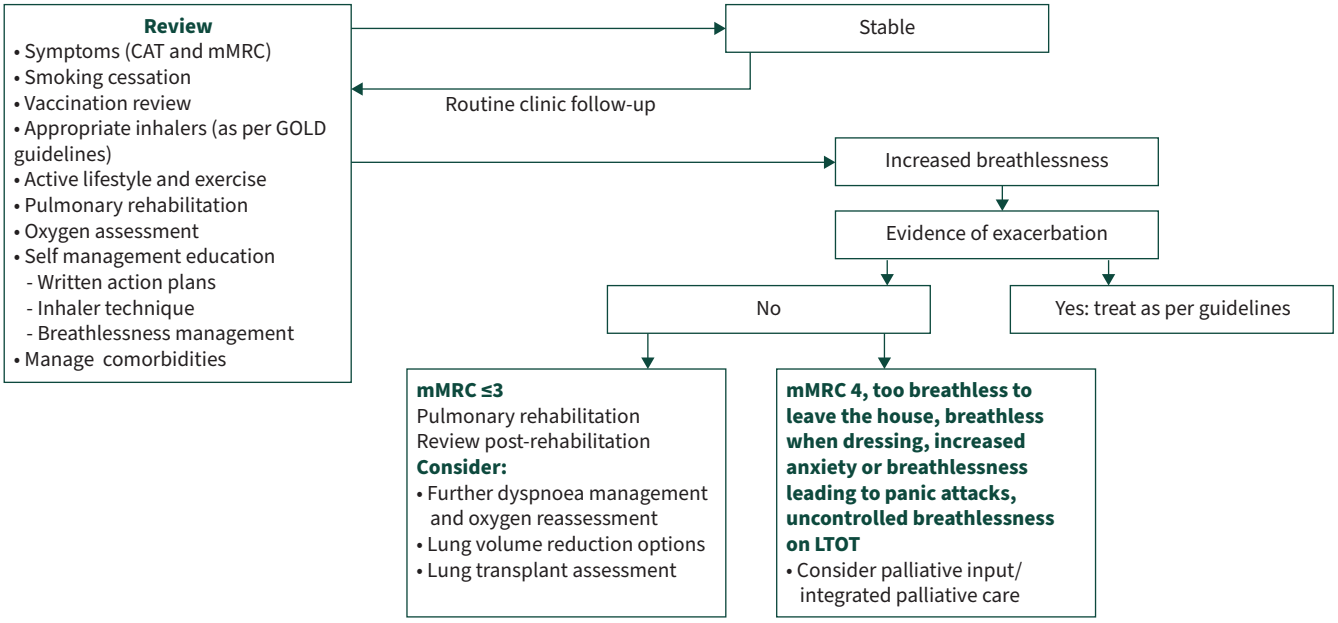

FIGURE 4 A proposed model for review of patients with advanced COPD including onward referral pathways. CAT: COPD Assessment Test; mMRC: modified Medical Research Council dyspnoea scale; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LTOT: long-term oxygen therapy.

advanced care planning. The pulmonary physician has a key role in recognising the requirement for palliative care in their patients but an integrated approach with the palliative team, with appropriate referral pathways in place, is optimal [81] (figure 4). Expert palliative input may be required for:

- Breathlessness having a very significant impact on the quality of life of the patient or family
- Multiple hospital admissions or consultations irrelevant to disease management
- Extra barriers exist to giving the patient and family excellent care
- Insufficient expertise within the respiratory service to provide adequate symptoms control

A large and growing body of evidence testifies to palliative care outcomes, that include improved patient satisfaction with care, decreased symptom burden and in some cases better survival [82]. Palliative care has been shown to create cost savings for health systems due to decreased hospital utilisation [83]. Incorporating palliative care earlier in the management of COPD patients and combining it with other therapy is suggested by the authors.

Areas for future research

There are areas for further research and service development within advanced COPD. More widespread support for oxygen therapy and NIV follow-up care may help with appropriate prescription and therapy compliance, to optimise this expensive resource for each patient. Studies are needed to clarify which patient cohorts may benefit from referral to transplant rather than LVR options. Within the area of lung transplant, work continues on donor organ preservation methods and reconditioning of lungs and a more focused approach is now being adopted with respect to the area of personalised medicine in immunosuppression treatments. Results are awaited from ongoing trials in the area of pharmacological management of dyspnoea. Ongoing collaboration with palliative care colleagues in combination with further training in this skill set for pulmonary specialists are likely to improve symptom management care for these patients.

Conclusions

Although the GOLD report offers an evidence-based guide to diagnosis and treatment in COPD, an individualised, multidisciplinary approach is required in patients with advanced COPD to address the chronic symptomatology associated with the condition. This should include assessment of oxygen requirement, review of the role of NIV, dyspnoea management coaching, and consideration of surgical or bronchoscopic options, up to and including lung transplantation, which can run in parallel with a palliative approach to chronic symptoms.

Key points

- Oxygen therapy reduces mortality in COPD patients with severe hypoxaemic respiratory failure.
- NIV is of benefit in some patients; NIV can improve admission-free survival in stable hypercapnic patients or persistently hypercapnic patients post-acute exacerbation of COPD.
- Physiotherapy and rehabilitation approaches can address dyspnoea management and improve exercise tolerance.
- Consideration of lung volume reduction *via* surgical or bronchoscopic approaches is appropriate for patients within set criteria.
- Lung transplantation assessment is appropriate for a subgroup of patients, but mortality benefit is not demonstrated.
- Symptom management with a palliative approach can run alongside the other treatments.

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References

1 World Health Organization. Burden of COPD. Geneva, World Health Organization, 2017. https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)
2 Disler RT, Green A, Luckett T, *et al.* Experience of advanced chronic obstructive pulmonary disease: metasynthesis of qualitative research. *J Pain Symptom Manage* 2014; 48: 1182–1199.
3 Gupta N, Malhotra N, Ish P. GOLD 2021 guidelines for COPD – what's new and why. *Adv Respir Med* 2021; 89: 344–346.
4 Tonnesen P. Smoking cessation and COPD. *Eur Respir Rev* 2013; 22: 37–43.
5 Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
6 Venkatesan P. GOLD report: 2022 update. *Lancet Respir Med* 2022; 10: e20.
7 Fishman A, Martinez F, Naunheim K, *et al.* A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059–2073.
8 Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980; 93: 391–398.
9 Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681–686.
10 Long-Term Oxygen Treatment Trial Research Group, Albert RK, Au DH, *et al.* A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med* 2016; 375: 1617–1627.
11 Branson RD. Oxygen therapy in COPD. *Respir Care* 2018; 63: 734–748.
12 Ekstrom M. Clinical usefulness of long-term oxygen therapy in adults. *N Engl J Med* 2016; 375: 1683–1684.
13 Campbell ML, Yarandi H, Dove-Medows E. Oxygen is nonbeneficial for most patients who are near death. *J Pain Symptom Manage* 2013; 45: 517–523.
14 Costello R, Deegan P, Fitzpatrick M, *et al.* Reversible hypercapnia in chronic obstructive pulmonary disease: a distinct pattern of respiratory failure with a favorable prognosis. *Am J Med* 1997; 102: 239–244.
15 Connors AF Jr, Dawson NV, Thomas C, *et al.* Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996; 154: 959–967.
16 McEvoy RD, Pierce RJ, Hillman D, *et al.* Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax* 2009; 64: 561–566.
17 Kohnlein T, Windisch W, Kohler D, *et al.* Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014; 2: 698–705.
18 Ergan B, Oczkowski S, Rochwerg B, *et al.* European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. *Eur Respir J* 2019; 54: 1901003.
19 Clini E, Sturani C, Rossi A, *et al.* The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; 20: 529–538.
20 Duiverman ML, Wempe JB, Bladder G, *et al.* Nocturnal non-invasive ventilation in addition to rehabilitation in hypercapnic patients with COPD. *Thorax* 2008; 63: 1052–1057.
21 Strumpf DA, Millman RP, Carlisle CC, *et al.* Nocturnal positive-pressure ventilation *via* nasal mask in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; 144: 1234–1239.
22 Gay PC, Hubmayr RD, Stroetz RW. Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. *Mayo Clin Proc* 1996; 71: 533–542.

23 Garrod R, Mikelsons C, Paul EA, *et al.* Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 1335–1341.
24 Casanova C, Celli BR, Tost L, *et al.* Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. *Chest* 2000; 118: 1582–1590.
25 Bhatt SP, Peterson MW, Wilson JS, *et al.* Noninvasive positive pressure ventilation in subjects with stable COPD: a randomized trial. *Int J Chron Obstruct Pulmon Dis* 2013; 8: 581–589.
26 Masefield S, Vitacca M, Dreher M, *et al.* Attitudes and preferences of home mechanical ventilation users from four European countries: an ERS/ELF survey. *ERJ Open Res* 2017; 3: 00015-2017.
27 Cheung AP, Chan VL, Liong JT, *et al.* A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis* 2010; 14: 642–649.
28 Struik FM, Sprooten RT, Kerstjens HA, *et al.* Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax* 2014; 69: 826–834.
29 Murphy PB, Rehal S, Arbane G, *et al.* Effect of home noninvasive ventilation with oxygen therapy *vs* oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA* 2017; 317: 2177–2186.
30 Lukacsovits J, Carlucci A, Hill N, *et al.* Physiological changes during low- and high-intensity noninvasive ventilation. *Eur Respir J* 2012; 39: 869–875.
31 Macrea M, Oczkowski S, Rochwerg B, *et al.* Long-term noninvasive ventilation in chronic stable hypercapnic chronic obstructive pulmonary disease. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* 2020; 202: e74–e87.
32 Hall J, Turner AM, Dretzke J, *et al.* Cost-effectiveness of domiciliary non-invasive ventilation in patients with chronic obstructive pulmonary disease. *Thorax* 2021; 77: 976–986.
33 Frat JP, Thille AW, Mercat A, *et al.* High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; 372: 2185–2196.
34 Veenstra P, Veeger N, Koppers RJH, *et al.* High-flow nasal cannula oxygen therapy for admitted COPD-patients. A retrospective cohort study. *PLoS ONE* 2022; 17: e0272372.
35 Longhini F, Pisani L, Lungu R, *et al.* High-flow oxygen therapy after noninvasive ventilation interruption in patients recovering from hypercapnic acute respiratory failure: a physiological crossover trial. *Crit Care Med* 2019; 47: e506–e511.
36 Fricke K, Tatkov S, Domanski U, *et al.* Nasal high flow reduces hypercapnia by clearance of anatomical dead space in a COPD patient. *Respir Med Case Rep* 2016; 19: 115–117.
37 Marciniuk DD, Goodridge D, Hernandez P, *et al.* Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. *Can Respir J* 2011; 18: 69–78.
38 O'Donnell DE, Milne KM, James MD, *et al.* Dyspnea in COPD: new mechanistic insights and management implications. *Adv Ther* 2020; 37: 41–60.
39 Parshall MB, Schwartzstein RM, Adams L, *et al.* An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; 185: 435–452.
40 Johnson MJ, Yorke J, Hansen-Flaschen J, *et al.* Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. *Eur Respir J* 2017; 49: 1602277.
41 Pryor JA, Prasad SA. Physiotherapy for Respiratory and Cardiac Problems: Adults and Paediatrics. 3rd Edn. London, Churchill Livingstone, 2002.
42 Dal Corso S, Napolis L, Malaguti C, *et al.* Skeletal muscle structure and function in response to electrical stimulation in moderately impaired COPD patients. *Respir Med* 2007; 101: 1236–1243.
43 Vieira PJ, Chiappa AM, Cipriano G Jr, *et al.* Neuromuscular electrical stimulation improves clinical and physiological function in COPD patients. *Respir Med* 2014; 108: 609–620.
44 Luckett T, Phillips J, Johnson MJ, *et al.* Contributions of a hand-held fan to self-management of chronic breathlessness. *Eur Respir J* 2017; 50: 1700262.
45 Kim HC, Mofarrahi M, Hussain SN. Skeletal muscle dysfunction in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2008; 3: 637–658.
46 Prefaut C. Activité physique et équilibre cardio-respiratoire [Physical activity and cardiorespiratory equilibrium]. *Bull Acad Natl Med* 1995; 179: 1461–1469.
47 McCarthy B, Casey D, Devane D, *et al.* Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; 2: CD003793.
48 Mador MJ, Rodis A, Magalang UJ. Reproducibility of Borg scale measurements of dyspnea during exercise in patients with COPD. *Chest* 1995; 107: 1590–1597.
49 British Thoracic Society. Quality Standards for Pulmonary Rehabilitation in Adults. London, British Thoracic Society, 2014. ISSN 2040-2023. www.brit-thoracic.org.uk/quality-improvement/quality-standards/pulmonary-rehabilitation/

50 van Agteren JE, Carson KV, Tiong LU, *et al.* Lung volume reduction surgery for diffuse emphysema. *Cochrane Database Syst Rev* 2016; 10: CD001001.
51 Lee M, Mora Carpio AL. Lung Volume Reduction Surgery. Treasure Island, StatPearls, 2021.
52 Beling J. Lung volume reduction surgery and pulmonary rehabilitation improve exercise capacity and reduce dyspnea during functional activities in people with emphysema. *Cardiopulm Phys Ther J* 2009; 20: 5–12.
53 Chew J, Mahadeva R. The role of a multidisciplinary severe chronic obstructive pulmonary disease hyperinflation service in patient selection for lung volume reduction. *J Thorac Dis* 2018; 10: Suppl. 27, S3335–S3343.
54 Ramsey SD, Blough DK, Sullivan SD. A forensic evaluation of the National Emphysema Treatment Trial using the expected value of information approach. *Med Care* 2008; 46: 542–548.
55 Clark SJ, Zoumot Z, Bamsey O, *et al.* Surgical approaches for lung volume reduction in emphysema. *Clin Med (Lond)* 2014; 14: 122–127.
56 Patel N, DeCamp M, Criner GJ. Lung transplantation and lung volume reduction surgery versus transplantation in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5: 447–453.
57 Shanahan B, Egan M, Murphy D, *et al.* Robot-Assisted Left Upper Lobe Lung Volume Reduction Surgery With Intraoperative Firefly Perfusion Assessment. CTSNet, 2019. https://doi.org/10.25373/ctsnet.7863440.v1
58 Abia-Trujillo D, Johnson MM, Patel NM, *et al.* Bronchoscopic lung volume reduction: a new hope for patients with severe emphysema and air trapping. *Mayo Clin Proc* 2021; 96: 464–472.
59 Mulryan K. An analysis of the economic benefits of introducing a network of chronic obstructive pulmonary disease (COPD) multi-disciplinary teams (MDTs) linked to lung volume reduction services in Ireland. Doctoral dissertation. Dublin, Royal College of Surgeons, 2022.
60 Gompelmann D, Benjamin N, Bischoff E, *et al.* Survival after endoscopic valve therapy in patients with severe emphysema. *Respiration* 2019; 97: 145–152.
61 Whittaker HR, Connell O, Campbell J, *et al.* Eligibility for lung volume reduction surgery in patients with COPD identified in a UK primary care setting. *Chest* 2020; 157: 276–285.
62 Weill D, Benden C, Corris PA, *et al.* A consensus document for the selection of lung transplant candidates: 2014 – an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2015; 34: 1–15.
63 Glanville AR, Estenne M. Indications, patient selection and timing of referral for lung transplantation. *Eur Respir J* 2003; 22: 845–852.
64 International Society for Heart and Lung Transplantation. International Thoracic Organ Transplant registry data slides. 2019. https://ishltregistries.org/registries/slides.asp?yearToDisplay=2019
65 Leard LE, Valapour M, Glanville AR, *et al.* Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2021; 40: 1349–1379.
66 Perch M, Cherikh WS, Zuckermann A, *et al.* Focus on lung transplant recipients with chronic obstructive pulmonary disease. *J Heart Lung Transplant* 2022: 41; 1335–1347.
67 Strutt R. When to refer patients with advanced COPD to palliative care services. *Breathe* 2020; 16: 200061.
68 Lanken PN, Terry PB, Delisser HM, *et al.* An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med* 2008; 177: 912–927.
69 Bloom CI, Slaich B, Morales DR, *et al.* Low uptake of palliative care for COPD patients within primary care in the UK. *Eur Respir J* 2018; 51: 1701879.
70 Han MK, Martinez CH, Au DH, *et al.* Meeting the challenge of COPD care delivery in the USA: a multiprovider perspective. *Lancet Respir Med* 2016; 4: 473–526.
71 Almagro P, Yun S, Sangil A, *et al.* Palliative care and prognosis in COPD: a systematic review with a validation cohort. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 1721–1729.
72 Abdallah SJ, Wilkinson-Maitland C, Saad N, *et al.* Effect of morphine on breathlessness and exercise endurance in advanced COPD: a randomised crossover trial. *Eur Respir J* 2017; 50: 1701235.
73 Verberkt CA, van den Beuken-van Everdingen MHJ, Schols J, *et al.* Effect of sustained-release morphine for refractory breathlessness in chronic obstructive pulmonary disease on health status: a randomized clinical trial. *JAMA Intern Med* 2020; 180: 1306–1314.
74 Simon ST, Higginson IJ, Booth S, *et al.* Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev* 2016; 10: CD007354.
75 Lovell N, Bajwah S, Maddocks M, *et al.* Use of mirtazapine in patients with chronic breathlessness: a case series. *Palliat Med* 2018; 32: 1518–1521.
76 Lovell N, Wilcock A, Bajwah S, *et al.* Mirtazapine for chronic breathlessness? A review of mechanistic insights and therapeutic potential. *Expert Rev Respir Med* 2019; 13: 173–180.
77 Higginson IJ, Wilcock A, Johnson MJ, *et al.* Randomised, double-blind, multicentre, mixed-methods, dose-escalation feasibility trial of mirtazapine for better treatment of severe breathlessness in advanced lung disease (BETTER-B feasibility). *Thorax* 2020; 75: 176–179.

78 Van Herck M, Antons J, Vercoulen JH, *et al.* Pulmonary rehabilitation reduces subjective fatigue in COPD: a responder analysis. *J Clin Med* 2019; 8: 1264.

79 McGarvey LP, Birring SS, Morice AH, *et al.* Efficacy and safety of gefapixant, a P2X3 receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet* 2022; 399: 909–923.

80 Morice AH, Menon MS, Mulrennan SA, *et al.* Opiate therapy in chronic cough. *Am J Respir Crit Care Med* 2007; 175: 312–315.

81 Higginson IJ, Bausewein C, Reilly CC, *et al.* An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014; 2: 979–987.

82 Maddocks M, Lovell N, Booth S, *et al.* Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *Lancet* 2017; 390: 988–1002.

83 Morrison RS, Penrod JD, Cassel JB, *et al.* Cost savings associated with US hospital palliative care consultation programs. *Arch Intern Med* 2008; 168: 1783–1790.