



REVIEW

Strategies to relieve dyspnoea in patients with advanced chronic respiratory diseases. A narrative review



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KEYWORDS

COPD;
Lung cancer;
Interstitial lung diseases;
Pulmonary rehabilitation;
Non invasive ventilation;
Opioids;
Oxygen;
High-flow nasal therapy;
Palliative care;
Integrated care

Abstract

Background and objective: The management of symptoms in patients with advanced chronic respiratory diseases needs more attention. This review summarizes the latest evidence on interventions to relieve dyspnoea in these patients.

Methods: We searched randomised controlled trials, observational studies, systematic reviews, and meta-analyses published between 1990 and 2019 in English in PubMed data base using the keywords. Dyspnoea, Breathlessness AND: pharmacological and non pharmacological therapy, oxygen, non invasive ventilation, pulmonary rehabilitation, alternative medicine, intensive care, palliative care, integrated care, self-management. Studies on drugs (e.g. bronchodilators) or interventions (e.g. lung volume reduction surgery, lung transplantation) to manage underlying conditions and complications, or tools for relief of associated symptoms such as pain, are not addressed.

Results: Relief of dyspnoea has received relatively little attention in clinical practice and literature. Many pharmacological and non pharmacological therapies are available to relieve dyspnoea, and improve patients' quality of life. There is a need for greater knowledge of the benefits and risks of these tools by doctors, patients and families to avoid unnecessary fears which might reduce or delay the delivery of appropriate care. We need services for multidisciplinary care in early and late phases of diseases. Early integration of palliative care with respiratory, primary care, and rehabilitation services can help patients and caregivers.

Conclusion: Relief of dyspnoea as well as of any distressing symptom is a human right and an ethical duty for doctors and caregivers who have many potential resources to achieve this.

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Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; CRD, chronic respiratory diseases; CWV, chest wall vibration; EoL, end of life; ERS, European Respiratory Society; HFNT, high-flow nasal therapy; HRQL, health related quality of life; ICU, intensive care unit; ILD, interstitial lung diseases; LTOT, long term oxygen therapy; NIV, non invasive ventilation; NMES, neuromuscular electrical stimulation; PaCO₂, arterial carbon dioxide tension; PaO₂, arterial oxygen tension; RCT, randomised controlled trial; WOB, work of breathing.

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Introduction

World Health Organization includes chronic respiratory diseases (CRD) among the 4 major human chronic diseases accounting for an estimated 7.5 million deaths per year, approximately 14% of annual deaths worldwide. These diseases are a major economic and human burden. The most frequent CRD include, in descending order, chronic obstructive pulmonary disease (COPD), lung cancer, tuberculosis, lung infections, asthma, and interstitial lung diseases (ILD).¹

Definition. Dyspnoea is defined as “the subjective experience of breathing discomfort”, and is a multidimensional symptom resulting from multiple mechanisms, reducing health related quality of life (HRQL) and leading to distress in patients and families in all stages of disease.²⁻⁴ Independent of the underlying disease the term “chronic breathlessness syndrome”, has been proposed and defined as “breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability”.⁵

Neurophysiological basis. The neurophysiological basis of this disabling symptom relies on receptors in the airways, lung parenchyma, respiratory muscles and in chemoreceptors providing sensory feedback via vagal, phrenic and intercostal nerves to the spinal cord, medulla and higher centres automatically adjusting breathing based on appraisal of blood gases, acid-base, and mechanical status of the respiratory system.^{2,6} Two common stimuli are hypoxaemia activating the carotid bodies and static and dynamic hyperinflation, which can activate mechanoreceptors in the lungs and respiratory muscle receptors. The central nervous system integrates and processes respiratory inputs from receptors. Neuroimaging shows that the anterior insular cortex, anterior cingulate cortex, amygdala, dorso-lateral prefrontal cortex, and cerebellum are activated in responses to stimuli.⁷

Descriptors and severity. The perception of dyspnoea is considered to result from an imbalance between the *demand to breathe* and the *ability to breathe*. This has been called “*neuromechanical dissociation*”.² Psychological factors such as anxiety, panic, and depression can also affect the experience of dyspnoea.⁸ Breathlessness in different CRD is based on different pathophysiological abnormalities leading to different qualities of respiratory discomfort, as defined by specific verbal descriptors associated to a specific diagnosis.^{3,9} Differences in languages, races, cultures, gender, and in how concepts or symptoms are considered can all influence the idea, description, quality and intensity of dyspnoea.⁹

Breathlessness is a sensation: severity cannot be predicted from lung function. There are “high perceivers” reporting higher than expected ratings based on objective data, and “low perceivers” reporting little if any breathing discomfort despite severe physiological impairment. Severe breathlessness may be present despite a normal lung function such as in cancer and absent in severe airway obstruction such as in resting stable COPD patients. Therefore dyspnoea must be assessed and measured specifically with the available tools in order to be able to evaluate the effects of any treatment.^{10,11} As shown in [Table 1](#) several instruments are commonly used to measure different

Table 1 Common instruments used to assess dyspnoea.

<i>Stimulus – Activities of Daily Living</i>
Baseline Dyspnea Index – Transition Dyspnea Index
Dyspnoea component of Chronic Respiratory Questionnaire
University of California San Diego Shortness of Breath Questionnaire
Medical Research Council Scale
<i>Stimulus – Exercise</i>
Modified Borg Scale
Visual Analog Scale

domains of dyspnoea such as sensory-perceptual experience, affective distress, symptom impact or burden.

Epidemiology. The management of dyspnoea in patients with CRD needs more attention in clinical practice and medical literature.^{12,13} Studies have estimated a 9–13% prevalence for mild to moderate dyspnoea among community-residing adults, 15–18% among those adults aged 40 years or older, and 25–37% of adults aged 70 years and older. Fifty to 70% of patients with cancer and 56–98% of patients with COPD complain of dyspnoea which causes up to half of admissions to Emergency Departments, and one quarter of out-patients visits (3–4 million annual visits). Furthermore dyspnoea, is an important predictor of outcomes indexes such as mortality, morbidity, time to clinical worsening, change in HRQL and exercise tolerance.¹⁴⁻¹⁹ As opposed to pain, in intensive care units (ICU) patients detection and management of dyspnoea have been neglected. Dyspnoea affects half of mechanically ventilated patients, it is associated with delayed extubation and with increased risk of intubation and mortality in those receiving non invasive ventilation (NIV). However, one-third of critically ill patients are unable to communicate, and therefore, at high risk of underestimation and undertreatment of symptoms. Inadequate ventilator settings seem to play a major role contributing to the pathogenesis of dyspnoea in this setting.²⁰⁻²²

Aim of the review. Pathogenetic therapy of underlying diseases is the cornerstone in management of dyspnoea. Unfortunately with progression of natural history, this approach may be not enough to face the increasing severity of this distressing symptom, requiring also a more specific approach. This narrative review summarizes the most recent evidences on symptomatic pharmacological and non pharmacological therapies for the management of dyspnoea in patients with advanced CRD either in stable state or at their end of life (EoL), independent of the underlying respiratory disease. Pathogenetic therapy of underlying diseases as well as other systemic contributors to dyspnoea in complex comorbid conditions, such as cardiovascular failure, anaemia, neuromuscular conditions or extreme cachexia will be not addressed.

Methods

We searched randomised controlled trials (RCT), observational studies, systematic reviews, and meta-analyses published in English between 1990 and 2019 in PubMed data base using the keywords: Dyspnoea, Breathlessness AND: pharmacological and non pharmacological therapy, oxygen,

non invasive ventilation, pulmonary rehabilitation, alternative medicine, intensive care, palliative care, integrated care, self-management.

Exclusion criteria. Studies on drugs (e.g. bronchodilators) or interventions (e.g. lung volume reduction surgery, lung transplantation) to manage the underlying conditions and complications, or tools for relief of coexisting symptoms contributing to breathlessness such as pain, are not addressed in this narrative review.

Pharmacological interventions

Opioids

When other pharmacological interventions are no longer effective in refractory breathlessness, opioids can still work in the most severe cases of advanced CRD and at EoL. Opioids relieve dyspnoea by action on central receptors in the right posterior cingulate gyrus of brain. Studies of different drugs (diamorphine, dihydrocodeine, morphine, fentanyl, oxycodone), formulations (nebulized, subcutaneous, oral), and schedule of administration (single vs multiple doses) in different conditions show low-quality evidence of benefit for the use of oral or parenteral opioids, in low doses.^{23–25} The evidence to support the use of nebulized opioids is unclear.^{23,25} We need to be aware of and treat adverse effects such as nausea, vomiting, and constipation.²⁶

A systematic review showed that morphine still has the best level of evidence for the symptomatic treatment of chronic breathlessness and international guidelines recommend the use of opioids in patients with advanced CRD.^{27–29} However, there are differences in attitudes towards opiates between patients and doctors and among doctors.

A study explored blinded patient preference for morphine compared to placebo. The majority of patients preferred morphine, the preference being influenced by adverse side effects but not by the intensity of breathlessness.³⁰ Some physicians prescribe opioids at EoL, but not in earlier stages of disease, despite systematic reviews showing lack of evidence of relevant respiratory adverse effects.^{31,32} In one survey, patients on opioids reported a sense of calm and relief from severe dyspnoea, improvements in anxiety and depression, reductions in their stress and improvements in HRQL, while family caregivers felt that opioids helped patients to breathe more “normally”.³³ In contrast most physicians were reluctant to prescribe opioids for refractory dyspnoea, due to lack of knowledge and experience with the drug, leading to fears of potential adverse effects and legal problems.³³ In another study palliative doctors recommended more short-acting oral morphine, compared to pulmonologists who had concerns about respiratory depression and lack of knowledge.³⁴ Furthermore a recent systematic review has shown that general practitioners felt more comfortable treating pain, rather than dyspnoea and depression when caring for terminal patients.³⁵ These discrepancies between the positive experiences of patients and family caregivers and reluctance of some physicians to prescribe opioids represent important obstacles in care and should be overcome by appropriate training and communication.

Benzodiazepines and antidepressants

Anxiety can result from and/or contribute to development and/or worsening of dyspnoea, with a stressful vicious circle, therefore anxiolytics might be helpful. A recent review examined the effects of benzodiazepines on the relief of breathlessness in patients with advanced cancer or COPD.³⁶ This analysis of literature did not discover any beneficial effects of benzodiazepines for the relief of breathlessness compared to placebo, midazolam, morphine, or promethazine. Nor was it found that they had any significant effect in preventing episodes of breathlessness in people with cancer compared to morphine. No significant differences among types of benzodiazepine, dose, route and frequency of delivery, duration of treatment were found. Benzodiazepines caused statistically significantly more adverse events, particularly drowsiness and somnolence, when compared to placebo. Authors concluded that benzodiazepines may be considered as a second- or third-line treatment, when opioids and non pharmacological measures have failed to control breathlessness.³⁶

Despite concerns about safety, benzodiazepines are used in combination with opioids to treat dyspnoea and related anxiety at the EoL, because the principle of double effect (potential shortening of life vs comfort) can ethically justify this approach. In a large population study benzodiazepines and opioids were not associated with increased hospital admissions. Benzodiazepines were associated with increased mortality in a dose response relationship.³⁷ Opioids also had a dose response relationship with mortality: daily doses lower than 30 mg oral morphine equivalents were not associated with increased mortality in contrast with higher doses. Combination of benzodiazepines and opioids in lower doses were not associated with increased admissions or mortality. Associations were not modified by being naïve about the drugs or by presence of hypercapnia.³⁷ A Swedish study examined the association of benzodiazepines and opioids with risk of hospital admissions and death in patients with ILD on long-term oxygen therapy (LTOT).³⁸ There was no association between benzodiazepines and increased admissions. Higher versus lower doses of benzodiazepines were associated with increased mortality. Opioids showed no association with increased admissions. Neither daily doses lower nor higher than 30 mg morphine equivalent showed association with increased mortality.³⁸

Depression commonly accompanies breathlessness, so there is a rationale for using antidepressants, because serotonergic pathways are involved in the genesis of the symptom. In palliative care scenario case series have shown reduced breathlessness following the use of mirtazapine (not a first-line antidepressant) in patients with advanced CRD.³⁹ These patients felt more in control of their breathing, and able to recover more quickly from episodes of breathlessness. Some cases also reported beneficial effects on anxiety, panic, appetite and sleep. No adverse effects were reported.³⁹ Systematic reviews on non-opioid medications including phenothiazines, concluded that there was insufficient evidence to support their routine use to control chronic breathlessness.^{27,40}

Standard oxygen

Long-term oxygen therapy improves survival in hypoxaemic stable COPD patients, but its role as a means to reduce severe breathlessness also in patients without hypoxia is still controversial.⁴¹ There is evidence that oxygen can relieve exercise but not daily life breathlessness or HRQL in COPD patients not qualified for LTOT.⁴²

The relief of symptoms might occur by reduction of the motor command output from the central controller, and in COPD patients by reduction in dynamic hyperinflation and in ventilatory requirement for a given work rate. Other possible mechanisms are reductions of hypoxaemia, serum lactic acid, and pulmonary artery pressure.^{2,43}

A RCT showed that there was no additional symptomatic benefit from oxygen over room air delivered by nasal cannulae for relieving refractory dyspnoea due to advanced diseases in patients with arterial oxygen tension (PaO₂) >55 mmHg.⁴⁴ Dyspnoea improved with supplemental oxygen as well as with air via nasal cannula. The interpretation was that both flows (air and oxygen) might stimulate upper airway receptors and reduce breathing drive, minute ventilation, and dyspnoea independently of any effect on PaO₂.⁴⁴ Another meta-analysis failed to find benefits for dyspnoea by standard oxygen in patients with cancer.⁴⁵

The use of supplemental oxygen during exercise to relieve dyspnoea in normoxic patients with ILD at rest and desaturating during exercise is still controversial: a meta-analysis in patients with idiopathic pulmonary fibrosis was inconclusive.⁴⁶ More recently a RCT has shown that oxygen at an inspiratory fraction 0.50 improved tolerance, oxygen saturation and dyspnoea.⁴⁷ In a multicenter prospective RCT in patients with fibrotic ILD, normoxaemic at rest but desaturating to 88% or less, ambulatory oxygen resulted in improved HRQL.⁴⁸

Despite its potential benefits, only half of the patients use LTOT for the prescribed number of hours per day. In routine practice, barriers to optimal use of oxygen include inability to meet at home the high-dose oxygen required by advanced CRD such as ILD, and concerns of physicians about risks of acute hypercapnia or lung damages due to oxidative stress. Caregivers find caring for patients with refractory breathlessness extremely distressing. They often overestimate the benefits of LTOT, whereas its potential harm is underestimated.⁴⁹ In some parts of the world, there are limitations for oxygen use: patients cannot afford the costs of liquid oxygen equipment or the increased electricity consumption associated with a home oxygen concentrator. Technology may help: electronic monitors have the potential to measure adherence to LTOT more precisely. For example, devices can sense respiratory-related pressure fluctuations within oxygen tubing, with a minute-by-minute assessment of oxygen use and related signals can be sent to a central monitor.⁵⁰

Other drugs

Steroids. Many physicians believe corticosteroids are useful in treating dyspnoea in terminal patients, mainly due to their antiinflammatory activity. A RCT of patients with cancer suggests that dexamethasone may be associated

with rapid improvement in dyspnoea and drowsiness and is well tolerated.⁵¹ However the evidence supporting use of systemic steroids as symptomatic drugs in palliation of dyspnoea is weak and should not be prescribed for dyspnoea where underlying severe airway or parenchymal lung involvement is not being of managed.

Furosemide. A RCT with healthy volunteers showed that inhaled furosemide was effective in relieving laboratory induced air hunger, the most unpleasant quality of dyspnoea, a finding not confirmed later even at higher doses.^{52,53} Nebulized furosemide has been tested as a novel approach to improving dyspnoea, however based on available data, its use for the routine management of dyspnoea in terminal patients is still controversial or not indicated.^{40,54}

Other drugs have been tested such as cannabinoids and heliox, but none can be recommended for management of dyspnoea, outside a clinical trial setting.⁵⁵⁻⁵⁷ In a RCT in adults with advanced COPD, single-dose inhalation of vapourised cannabis had no clinically meaningful effect on airway function or exercise breathlessness and endurance.⁵⁶ Due to the low density, inert nature, strong safety profile and multiple applications of heliox, the potential benefits of helium-oxygen gas mixtures have been explored. A systematic review evaluated the effect of heliox inhalation on levels of dyspnoea and exercise performance in COPD.⁵⁷ Overall, there was high level of evidence of effectiveness in improving the intensity and endurance of exercise when compared to room air for people with COPD. However little conclusive evidence was found to determine whether heliox altered the sensation of dyspnoea during exercise.⁵⁷

Non-pharmacological interventions

Non invasive ventilation

There is no need of further evidence for the use of NIV for acute respiratory failure due to COPD exacerbations.⁵⁸ A multicentric study quantified the prevalence, intensity and prognostic impact of dyspnoea in patients receiving NIV for acute respiratory failure. Dyspnoea improved after the first NIV session and high levels of dyspnoea were associated with a higher risk of NIV failure and poorer outcome.⁵⁹

Long-term NIV is also effective in the management of chronic respiratory failure due to neuromuscular or restrictive thoracic diseases, whereas benefits from long-term NIV for stable hypercapnic COPD are not well-established, although outcomes may be improved with higher inspiratory pressure levels aimed at normalising arterial CO₂ tension (PaCO₂).⁶⁰ In stable hypercapnic COPD patients, long-term NIV plus LTOT was able to improve dyspnoea compared to LTOT alone.⁶¹

Non invasive ventilation can reduce breathlessness by improving oxygenation, ventilation, resistive load on the ventilatory muscles, dynamic hyperinflation, and WOB. In patients with COPD, NIV during exercise unloads the dysfunctional inspiratory muscles with an inspiratory positive airway pressure and reduces the dynamic hyperinflation and WOB with an expiratory positive airway pressure or with continuous positive airway pressure relieving dyspnoea.⁶²

In the EoL scenario a task force of the Society of Critical Care Medicine for the use of NIV in palliative care

settings identified distinct scenarios: (1) the patient has decided to forego intubation, but wants to receive NIV with the goal of surviving the hospitalization, and (2) the patient seeks symptom alleviation, mainly dyspnoea, but survival is not a realistic goal.⁶³ A RCT suggests that NIV is more effective than standard oxygen in reducing dyspnoea and decreasing the doses of morphine needed by patients with end-stage solid cancer.⁶⁴ A recent meta-analysis shows that many patients with do-not-intubate orders who receive NIV survive to hospital discharge.⁶⁵ However, despite favourable reports, the NIV European Respiratory Society (ERS)/American Thoracic Society (ATS) Task Force suggested that the small number of studies, the heterogeneity in trial design, and the relatively low acceptance rate prevent a firm recommendation regarding the use of NIV as a palliative tool.⁵⁸

High-flow nasal therapy

High-flow nasal therapy (HFNT) may provide beneficial effects, such as maintaining the integrity of mucociliary function by delivering heated and humidified gas at body conditions. Patients can also benefit from CO₂ washout by reduction in dead space.³ This modality also increases the end expiratory pressure and reduces respiratory rate resulting in reduction in the work of breathing (WOB) in patients with hypoxaemic respiratory failure or chronically hypercapnic COPD.^{66,67}

High-flow nasal therapy may improve exercise performance in severe COPD patients with ventilatory limitation.⁶⁸ A preliminary study evaluated the potential of HFNT for management of breathlessness in patients with cancer: most patients usually improved or remained stable, only a minority worsened.⁶⁹ However a cross over RCT has shown that six weeks of HFNT plus LTOT improved HRQL and reduced hypercapnia but not dyspnoea compared to LTOT alone in patients with stable hypercapnic COPD. Nocturnal sweating was the most frequent adverse event with HFNT.⁷⁰ In adult patients with cystic fibrosis with indication for ventilatory support, neither HFNT nor NIV had any effect on WOB, but HFNT was associated with decreased respiratory rate and minute ventilation, but not with improvement in dyspnoea.⁷¹

Pulmonary rehabilitation

Pulmonary rehabilitation, a multidisciplinary approach, has stronger evidence of effectiveness in improving exercise capacity, dyspnoea, and HRQL than almost all other therapies in patients with COPD including those with very severe disease, complex comorbidities and different phenotypes, and with a lower level of evidence in other CRD.⁷²⁻⁷⁶ Therefore current guidelines, recommend pulmonary rehabilitation for these patients.^{76,77} Some programs offer aerobic exercise or a combination of aerobic and resistance training, some also include education, nutritional advice, stress management and psychosocial support. In-hospital, outpatient and home programs range from 4 to 12 weeks, with two or more weekly supervised sessions. Evidence-based education addressing tailored maintenance regimens are needed to improve long-term outcomes.⁷⁸ Examples of components of pulmonary rehabilitation are shown in Table 2.

Benefits of pulmonary rehabilitation are often greater than those seen with other medical therapies and in COPD patients despite lack of improvements in lung function tests. In fact this intervention also addresses the systemic effects of CRD, including peripheral muscle dysfunction, physical inactivity leading to deconditioning, anxiety and depression, and negative behaviours such as a sedentary lifestyle and poor adherence to prescribed therapies. Potential mechanisms of dyspnoea relief following pulmonary rehabilitation include reduced central motor drive related to decreased metabolic acidosis, slower breathing pattern, reduced dynamic lung hyperinflation, increased function of the respiratory muscles, desensitization to dyspnoea-related fear and anxiety. Increased self-efficacy, improved emotional functioning and coping skills are also all thought to be fundamental contributors.⁷⁶

Randomised controlled trials of low to moderate quality have evaluated the efficacy of pulmonary rehabilitation in ILD.⁷⁹ Most components and clinical benefits of pulmonary rehabilitation in exercise capacity, dyspnoea and HRQL are similar to those for patients with COPD.⁸⁰ The ATS guidelines for management of idiopathic pulmonary fibrosis make a weak recommendation for pulmonary rehabilitation and the ATS/ERS statement on pulmonary rehabilitation also supports its use.^{76,81}

Table 2 Examples of interventions and outcome measures of pulmonary rehabilitation.

Components of training	Modalities
Aerobic	<i>Tool:</i> bike, treadmill; <i>Time:</i> 30–40 minutes per session; <i>Modality:</i> Continuous or interval training; <i>Intensity:</i> According to level of dyspnoea; <i>Schedule:</i> Progressed weekly
Resistance	<i>Tools:</i> Free weights, Elastic bands, Functional tasks/body weight – sit to stand, stair climbing, squats, wall push ups <i>Schedule:</i> sets of repetitions, major muscle groups of upper and lower limbs
Others	Flexibility, Nutrition, Stress Management, Education, Psychosocial support, Pedometers
Monitoring	Pulse oximetry, symptoms, Tele-rehabilitation
Schedule	4–12 weeks, 2–5 weekly supervised sessions
Outcome measures	Exercise capacity; Dyspnoea; Quality of life

There are some problems in practical delivery of pulmonary rehabilitation such as the high number of patients, difficult access to health facilities and high costs of programs; patients and providers may be unaware of potential benefits or reluctant to initiate this modality; in many practice settings, finding a program to accept the patient can be difficult. Tele-rehabilitation may be a solution: patients may perform exercises at home under supervision of a physiotherapist prescribing and changing programs and settings at distance.^{50,82} Alternatively the pedometers may incentivate spontaneous physical activity.⁸³

Oxygen during exercise

The role of oxygen during exercise training in well conducted pulmonary rehabilitation programs in COPD patients without hypoxaemia is still debated.⁷² In ILD during exercise oxygen desaturation is frequent and often more severe than in other CRD and pulmonary hypertension may worsen. Therefore pulmonary rehabilitation for ILD patients must be performed only when supplemental oxygen is available by an experienced staff. In most rehabilitation programs supplemental oxygen is safely administered during exercise to maintain pulse oxymetry above 85–90%.⁸⁰ However, a systematic review showed no effects of oxygen therapy on dyspnoea during exercise, although exercise capacity was increased.⁸⁴

Exercise and non invasive ventilation

Assisted ventilation is increasingly used during exercise training programs in order to train patients at intensity levels higher than allowed by their clinical and pathophysiological conditions.⁸⁵ This, may help to extend "personalised" sequential levels of pulmonary rehabilitation to most severe patients.⁸⁶ NIV assisted exercise training may be indicated for patients with COPD, with severe clinical and/or physiological conditions as assessed by the level of dyspnoea, airway obstruction or PaCO₂.⁸⁷ An individually tailored pulmonary rehabilitation program plus nighttime NIV patients significantly improved exercise capacity and HRQL also in hypercapnic ILD.⁸⁸

There are potential problems using NIV in exercise training (Table 3).⁸⁵

During high-intensity exercise patients may require a full-face mask or a mouthpiece potentially reducing compliance to the procedure.

The relief of exercise breathlessness associated to this modality might lead patients with unrecognised cardiac ischaemia to exercise at a load higher than their coronary ischaemic threshold.

This procedure requires a greater time consumption by physiotherapists and the increased physiotherapist to patient ratio as compared to standard rehabilitation increases the costs.

Other interventions

Neuromuscular electrical stimulation (NMES) may be an effective treatment for muscle weakness in adults with advanced CRD, and could be considered for use within rehabilitation programs.⁸⁹ A recent analysis showed that NMES, when applied in isolation, increased quadriceps force and endurance, walking test and time to symptom limitation exercising at a submaximal intensity, and reduced the severity of leg fatigue on completion of exercise testing.⁹⁰

Recent findings suggest that the use of a hand-held fan is a beneficial intervention for most patients with malignant and non malignant conditions and chronic breathlessness.⁹¹ It has been reported that in COPD patients, dyspnoea was modestly improved while listening to music and there was increased tolerance of high-intensity exercise.⁹²

A Cochrane review assessed other non pharmacological interventions to treat dyspnoea: walking aids, distractive auditory stimuli, cognitive therapy chest wall vibration (CWV), acupuncture/acupressure, relaxation, NMES, fans, and several multicomponent interventions.⁹³ There was evidence that CWV could relieve breathlessness and a lesser level of evidence for the use of walking aids and breathing training. There was a low level of evidence that acupuncture/acupressure is helpful. There were not enough data to judge the evidence for distractive auditory stimuli (music), relaxation, fan, counselling and support, breathing-relaxation training, case management and psychotherapy. Most studies have been conducted with COPD patients, only a few studies included participants with other CRD.⁹³ Another more recent systematic review of therapies such as acupressure, acupuncture, aroma therapy, massage, breathing, hypnotherapy, meditation, music therapy, reflexology, and reiki showed that many studies demonstrated a short-term benefit in symptom improvement with complementary or alternative medicine, without a significant benefit advantage compared to controls.⁹⁴

Table 3 Potential problems and solutions of exercise with NIV.⁸⁴

Source	Problems	Potential Solutions
Ventilator setting and interfaces	Haemodynamic effects of intrathoracic pressures Leaks CO ₂ rebreathing with single limb circuit Asynchronies	Preliminary evaluation of cardiac function; Face masks, Mouthpieces; Double limb circuit; Proportional ventilation modes
Comorbidities	Exercising at loads higher than coronary ischaemic threshold	Careful pre-exercise assessment
Organization issues	Workload of physiotherapists Supervision at home	Portable ventilators; Tele-monitoring

Multidisciplinary support services

Knowing the main concerns of patients with breathlessness and the positive effect of communication between doctors and patients is crucial for comprehensive clinical assessment and outcome measurement in clinical practice and research. Patients have their reasons for being upset, worried, frightened by the intensity of their dyspnoea; explaining the physiology and the reason why they feel so miserable, and that breathlessness per se is not dangerous, is a very important aspect of care. A systematic review identified six domains of "total" breathlessness: physical, emotional, spiritual, social, control, and context (chronic and episodic breathlessness).⁹⁵ Control and context were identified as important, particularly in their influence on coping and help-seeking behaviour. The importance of social participation, impact on relationships, and loss of perceived role within social and spiritual domains also were significant to patients.⁹⁵

When questioned, patients reported strategies for coping with episodes of breathlessness: reduction of physical exertion, cognitive and psychological strategies, breathing techniques and positions, air and oxygen, drugs and medical devices, and environmental and other strategies.⁹⁶ Supporting patients to self-manage can increase the patient's self-efficacy and reduce feelings of helplessness in both patients and caregivers. This may result in a virtuous circle of reduced anxiety and depression, more physical and daily life activity and social contact, with improved HRQL.²⁶

Holistic services are emerging, designed specifically for patients with advanced disease and chronic breathlessness. These services are typically based on palliative care cooperating with different specialities and professional groups. Treatments are selected based on the physical, psychological, social and spiritual needs of the individual patient, his/her family or carers. A systematic review has shown that these holistic services can reduce distress in patients with advanced disease and may improve anxiety and depression.⁹⁷

In a recent RCT of patients with advanced COPD, cancer, and ILD, as compared to usual care, dyspnoea and survival were improved by a multidisciplinary breathlessness support service, involving respiratory medicine, physiotherapy, occupational therapy, and palliative care.⁹⁸ At EoL optimal management of symptoms requires different skills by a health-care team, according to local resources, cultural factors, and religious beliefs of patients and caregivers.⁹⁹

When facing the management of dyspnoea, a strategy of increasingly aggressive interventions can be planned according to the increasing severity of symptoms or the stage of natural evolution of disease^{28,29}:

1. Therapy of underlying disease (e.g. in COPD: optimization of bronchodilators, LTOT, NIV according to guidelines⁷⁷);
2. Pulmonary rehabilitation with or without oxygen and/or NIV;
3. Palliative oxygen and/or pharmacological interventions (opioids, anxiolytics).

Early integration of palliative care with respiratory, primary care, and rehabilitation services taking into account the complexity of symptoms, rather than the estimated prognosis, should be the core of dyspnoea management in advanced CRD.¹⁰⁰ Early integration may give time to establish relationships between palliative care staff and patient/family and avoid problems of management during impending death.^{26,101} Unfortunately such services are still underutilized.^{102,103}

There is the need for individualized management plans. A study has evaluated the efficacy and acceptability of an intervention for COPD patients with refractory breathlessness.¹⁰⁴ The plan included information leaflets, education and a hand-held fan. There was an improvement in breathlessness severity. A subset of patients with anxiety/depression also reported significant improvements. Patients reported that the intervention was highly useful and acceptable.¹⁰⁴ However clear benefits from self management strategies are still to be demonstrated.¹⁰⁵⁻¹⁰⁷

Conclusion

Many pharmacological and non pharmacological therapies are now available to relieve dyspnoea, and improve patients' quality of life. Unfortunately there is the risk that unreasonable fears, mainly due to lack of knowledge of benefits and risks of these therapies result in loss of opportunities to improve patient care. This review may contribute to the knowledge of some available tools. Avoidance of dyspnoea as well as of any distressing symptom is a human right.

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Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Glass RI, Rosenthal JP. International Approach to Environmental and Lung Health. A Perspective from the Fogarty International Center. *Ann Am Thorac Soc.* 2018;15 Supplement_2:S109-13.
2. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med.* 2012;185:435-52.
3. Pisani L, Hill NS, Pacilli AMG, Polastri M, Nava S. Management of dyspnea in the terminally ill. *Chest.* 2018;154:925-34.
4. Vitacca M, Grassi M, Barbano L, Galavotti G, Sturani C, Vianello A, et al. Last 3 months of life in home-ventilated patients: the family perception. *Eur Respir J.* 2010;35:1064-71.
5. Johnson MJ, Yorke J, Hansen-Flaschen J, Lansing R, Ekström M, Similowski T, et al. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. *Eur Respir J.* 2017;49, pii: 1602277.
6. Mahler DA, O'Donnell DE. Neurobiology of dyspnea: an overview. In: Mahler DA, O'Donnell DE, editors. *Dyspnea:*

- mechanisms, measurement, and management. 3rd ed. Boca Raton, FL: CRC Press, Taylor & Francis Group; 2014. p. 3–10.
7. Evans KC, Banzett RB. Neuroimaging of dyspnea. In: Mahler DA, O'Donnell DE, editors. *Dyspnea: mechanisms, measurement, and management*. 3rd ed. Boca Raton, FL: CRC Press, Taylor & Francis Group; 2014. p. 3–10.
 8. Laviolette L, Laveneziana P. Dyspnoea: a multidimensional and multidisciplinary approach. *Eur Respir J*. 2014;43:1750–62.
 9. Mahler DA, Harver A, Lentine T, Scott JA, Beck K, Schwartzstein RM. Descriptors of breathlessness in cardiorespiratory diseases. *Am J Resp Crit Care Med*. 1996;154:1357–63.
 10. Mahler DA. Measurement of dyspnea: clinical ratings. In: Mahler DA, O'Donnell DE, editors. *Dyspnea: mechanisms, measurement, and management*. 2nd ed. Boca Raton, FL: Taylor & Francis Group; 2005. p. 147–66.
 11. Mahler DA. Evaluation of dyspnea in the elderly. In: Braman SS, Skloot GS, editors. *Pulmonary disease in the aging patient*. Philadelphia: Clinics in Geriatric Medicine; 2017. p. 503–21.
 12. Ekström MP, Abernethy AP, Currow DC. The management of chronic breathlessness in patients with advanced and terminal illness. *BMJ*. 2015;350:g7617.
 13. Currow DC, Abernethy AP, Allcroft P, Banzett RB, Bausewein C, Booth S, et al. The need to research refractory breathlessness. *Eur Respir J*. 2016;47:342–3.
 14. Berraho M, Nejjari C, El Rhazi K, Tessier JF, Dartigues JF, Barberger-Gateau P, et al. A strong independent factor for long-term mortality in the elderly. *J Nutr Health Aging*. 2013;17:908–12.
 15. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest*. 2002;121:1434–40.
 16. Hellenkamp K, Darius H, Giannitsis E, Erbel R, Haude M, Hamm C, et al. The German CPU registry: dyspnea independently predicts negative short-term outcome in patients admitted to German chest pain units. *Int J Cardiol*. 2015;181:88–95.
 17. Thomas S, Bausewein C, Higginson I, Booth S. Breathlessness in cancer patients – implications, management and challenges. *Eur J Oncol Nurs*. 2011;15:459–69.
 18. Laribi S, Keijzers G, van Meer O, Klim S, Motiejunaite J, Kuan WS, et al. Epidemiology of patients presenting with dyspnea to emergency departments in Europe and the Asia-Pacific region. *Eur J Emerg Med*. 2018 Aug;30, <http://dx.doi.org/10.1097/MEJ.0000000000000571> [Epub ahead of print].
 19. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350:1005–12.
 20. Decavèle M, Similowski T, Demoule A. Detection and management of dyspnea in mechanically ventilated patients. *Curr Opin Crit Care*. 2019;25:86–94.
 21. Gentzler ER, Derry H, Ouyang DJ, Lief L, Berlin DA, Xu CJ, et al. Underdetection and undertreatment of dyspnea in critically ill patients. *Am J Respir Crit Care Med*. 2018 Nov;28, <http://dx.doi.org/10.1164/rccm.201805-0996OC> [Epub ahead of print].
 22. Johnson MJ, Hutchinson A. Breathlessness in the emergency care setting. *Curr Opin Support Palliat Care*. 2018;12:232–6.
 23. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev*. 2016;3:CD011008.
 24. Yamaguchi T, Matsuda Y, Matsuoka H, Hisanaga T, Osaka I, Watanabe H, et al. Efficacy of immediate-release oxycodone for dyspnoea in cancer patient: cancer dyspnoea relief (CDR) trial. *Jpn J Clin Oncol*. 2018;48:1070–5.
 25. Ekström M, Bajwah S, Bland JM, Currow DC, Hussain J, Johnson MJ. One evidence base; three stories: do opioids relieve chronic breathlessness? *Thorax*. 2018;73:88–90.
 26. Maddocks M, Lovell N, Booth S, Man W, Higginson D-CIJ. Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *Lancet*. 2017;390:988–1002.
 27. Barbetta C, Currow DC, Johnson MJ. Non-opioid medications for the relief of chronic breathlessness: current evidence. *Expert Rev Respir Med*. 2017;11:333–41.
 28. Mahler DA, Selecky PA, Harrod CG, Benditt JO, Carrieri-Kohlman V, Curtis JR, et al. American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. *Chest*. 2010;137:674–91.
 29. Marciniuk DD, Goodridge D, Hernandez P, Rocker G, Balter M, Bailey 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.
 30. Ferreira DH, Silva JP, Quinn S, Abernethy AP, Johnson MJ, Oxberry SG, et al. Blinded patient preference for morphine compared to placebo in the setting of chronic refractory breathlessness. An exploratory study. *J Pain Symptom Manage*. 2016;51:247–54.
 31. Hadjiphilippou S, Odogwu SE, Dand P. Doctors' attitudes towards prescribing opioids for refractory dyspnoea: a single-centred study. *BMJ Support Palliat Care*. 2014;4:190–2.
 32. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMGA, Datla S, Dirksen CD, Johnson MJ, et al. Respiratory adverse effects of opioids for breathlessness: a systematic review and metaanalysis. *Eur Respir J*. 2017;50, pii: 1701153.
 33. Rocker G, Young J, Donahue M, Farquhar M, Simpson C. Perspectives of patients, family caregivers and physicians about the use of opioids for refractory dyspnea in advanced chronic obstructive pulmonary disease. *CMAJ*. 2012;184:E497–504.
 34. Smallwood N, Currow D, Booth S, Spathis A, Irving L, Philip J. Differing approaches to managing the chronic breathlessness syndrome in advanced COPD: a multi-national survey of specialists. *COPD*. 2018;15:294–302.
 35. Mitchell GK, Senior HE, Johnson CE, Fallon-Ferguson J, Williams B, Monterosso L, et al. Systematic review of general practice end-of-life symptom control. *BMJ Support Palliat Care*. 2018;8:411–20.
 36. Simon ST, Higginson IJ, Booth S, Harding R, Weingartner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev*. 2016;10:CD007354.
 37. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ*. 2014;348:g445.
 38. Bajwah S, Davies JM, Tanash H, Currow DC, Oluyase AO, Ekström M. Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study. *Eur Respir J*. 2018;52, pii: 1801278.
 39. Lovell N, Bajwah S, Maddocks M, Wilcock A, Higginson IJ. Use of mirtazapine in patients with chronic breathlessness: a case series. *Palliat Med*. 2018;32:1518–21.
 40. Awan S, Wilcock A. Nonopioid medication for the relief of refractory breathlessness. *Curr Opin Support Palliat Care*. 2015;9:227–31.
 41. Jindal SK, Agarwal R. Long-term oxygen therapy. *Expert Rev Respir Med*. 2012;6:639–49.
 42. Ekström M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D. Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not

- qualify for home oxygen therapy. *Cochrane Database Syst Rev.* 2016;11:CD006429.
43. Tiep B, Carter R. Long-term oxygen therapy. In: Donner CF, Ambrosino N, Goldstein R, editors. *Pulmonary rehabilitation*. Hodder (pub.); 2005. p. 312–20.
 44. Abernethy AP, McDonald CF, Frith PA, Clark K, Herndon JE 2nd, Marcello J, et al. Effect of palliative oxygen versus medical (room) air in relieving breathlessness in patients with refractory dyspnea: a double blind randomized controlled trial. *Lancet.* 2010;376:784–93.
 45. Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer SM. Interventions for alleviating cancer-related dyspnea: a systematic review and meta-analysis. *Acta Oncol.* 2012;51:996–1008.
 46. Sharp C, Adamali H, Millar AB. Ambulatory and short burst oxygen for interstitial lung disease. *Cochrane Database Syst Rev.* 2016;7:CD011716.
 47. Dowman LM, McDonald CF, Bozinovski S, Vlahos R, Gillies R, Pouniotis D, et al. Greater endurance capacity and improved dyspnoea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxaemia. *Respirology.* 2017;22:957–64.
 48. Visca D, Mori L, Tsipouri V, Fleming S, Firouzi A, Bonini M, et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. *Lancet Respir Med.* 2018;6:759–70.
 49. Collier A, Breaden K, Phillips JL, Agar M, Litster C, Currow DC. Caregivers' perspectives on the use of long-term oxygen therapy for the treatment of refractory breathlessness: a qualitative study. *J Pain Symptom Manage.* 2017;53:33–9.
 50. Donner CF, Raskin J, ZuWallack R, Nici L, Ambrosino N, Balbi B, et al. Incorporating telemedicine into the integrated care of the COPD patient a summary of an interdisciplinary workshop held in Stresa, Italy, 7–8 September 2017. *Respir Med.* 2018;143:91–102.
 51. Hui D, Kilgore K, Frisbee-Hume S, Park M, Tsao A, Delgado Guay M, et al. Dexamethasone for dyspnea in cancer patients: a pilot double-blind, randomized, controlled trial. *J Pain Symptom Manage.* 2016;52:8–16.
 52. Grogono JC, Butler C, Izadi H, Moosavi SH. Inhaled furosemide for relief of air hunger versus sense of breathing effort: a randomized controlled trial. *Respir Res.* 2018;19:181.
 53. Banzett RB, Schwartzstein RM, Lansing RW, O'Donnell CR. Aerosol furosemide for dyspnea: high-dose controlled delivery does not improve effectiveness. *Respir Physiol Neurobiol.* 2018;247:24–30.
 54. Boyden JY, Connor SR, Otolorin L, Nathan SD, Fine PG, Davis MS, et al. Nebulized medications for the treatment of dyspnea: a literature review. *J Aerosol Med Pulm Drug Deliv.* 2015;28:1–19.
 55. Martinasek MP, McGrogan JB, Maysonet A. A systematic review of the respiratory effects of inhalational marijuana. *Respir Care.* 2016;61:1543–51.
 56. Abdallah SJ, Smith BM, Ware MA, Moore M, Li PZ, Bourbeau J, et al. Effect of vaporized cannabis on exertional breathlessness and exercise endurance in advanced chronic obstructive pulmonary disease. A randomized controlled trial. *Ann Am Thorac Soc.* 2018;15:1146–58.
 57. Hunt T, Williams MT, Frith P, Schembri D. Heliox, dyspnoea and exercise in COPD. *Eur Respir Rev.* 2010;19:30–8.
 58. Rochweg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J.* 2017;50, pii: 1602426.
 59. Dangers L, Montlahuc C, Kouatchet A, Jaber S, Meziani F, Perbet S, et al. Dyspnoea in patients receiving noninvasive ventilation for acute respiratory failure: prevalence, risk factors and prognostic impact: a prospective observational study. *Eur Respir J.* 2018;52, pii: 1702637.
 60. Windisch W, Geiseler J, Simon K, Waltersbacher S, Dreher M, on behalf of the Guideline Commission. German national guideline for treating chronic respiratory failure with invasive and non-invasive ventilation: revised edition 2017 – Part 1. *Respiration.* 2018;96:66–97.
 61. Cline E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, et al. The Italian multicentre study on non invasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J.* 2002;20:529–38.
 62. O'Donnell DE, Sani R, Younes M. Improvement in exercise endurance in patients with chronic airflow limitation using continuous positive airway pressure. *Am Rev Respir Dis.* 1988;138:1510–4.
 63. Curtis JR, Cook DJ, Sinuff T, White DB, Hill N, Keenan SP, et al. Noninvasive positive pressure ventilation in critical and palliative care settings: understanding the goals of therapy. *Crit Care Med.* 2007;35:932–9.
 64. Nava S, Ferrer M, Esquinas A, Scala R, Groff P, Cosentini R, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. *Lancet Oncol.* 2013;14:219–27.
 65. Wilson ME, Majzoub AM, Dobler CC, Curtis JR, Nayfeh T, Thorsteinsdottir B, et al. Noninvasive ventilation in patients with do-not-intubate and comfort-measures-only orders: a systematic review and meta-analysis. *Crit Care Med.* 2018;46:1209–16.
 66. Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med.* 2017;195:1207–15.
 67. Pisani L, Fasano L, Corcione N, Comellini V, Musti MA, Brandao M, et al. Change in pulmonary mechanics and the effect on breathing pattern of high flow oxygen therapy in stable hypercapnic COPD. *Thorax.* 2017;72:373–5.
 68. Cirio S, Piran M, Vitacca M, Piaggi G, Cergiana P, Prazzoli M, et al. Effects of heated and humidified high flow gases during high-intensity constant-load exercise on severe COPD patients with ventilatory limitation. *Respir Med.* 2016;118:128–32.
 69. Epstein AS, Hartridge-Lambert SK, Ramaker JS, Voigt LP, Portlock CS. Humidified high-flow nasal oxygen utilization in patients with cancer at Memorial Sloan-Kettering Cancer Center. *J Palliat Med.* 2011;14:835–9.
 70. Nagata K, Kikuchi T, Horie T, Shiraki A, Kitajima T, Kadowaki T, et al. Domiciliary high-flow nasal cannula oxygen therapy for patients with stable hypercapnic chronic obstructive pulmonary disease. A multicenter randomized crossover trial. *Ann Am Thorac Soc.* 2018;15:432–9.
 71. Sklar MC, Dres M, Rittayamai N, West B, Grieco DL, Telias I, et al. High-flow nasal oxygen versus noninvasive ventilation in adult patients with cystic fibrosis: a randomized crossover physiological study. *Ann Intensive Care.* 2018;8:85.
 72. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2015;2:CD003793.
 73. Paneroni M, Simonelli C, Vitacca M, Ambrosino N. Aerobic exercise training in very severe COPD: a systematic review and meta-analysis. *Am J Phys Med Rehabil.* 2017;96:541–8.
 74. Griffo R, Spanevello A, Temporelli PL, Faggiano P, Carone M, Magni G, et al. Frequent coexistence of chronic heart failure and chronic obstructive pulmonary disease in respiratory and cardiac outpatients: evidence from SUSPIRIUM, a multicentre Italian survey. *Eur J Prev Cardiol.* 2017;24:567–76.
 75. Ambrosino N, Venturelli E, de Blasio F, Paggiaro P, Pasqua F, Vitacca M, et al. A prospective multicentric study of pulmonary rehabilitation in patients with chronic obstructive

- pulmonary disease and different clinical phenotypes. *Respiration*. 2015;89:141–7.
76. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188:e13–64.
 77. Global strategy for prevention, diagnosis and management of COPD; 2019. <http://goldcopd.org/gold-reports/> [accessed 01.01.9].
 78. Make BJ, Yawn BP. Breathing life into COPD management: ongoing monitoring, pulmonary rehabilitation, and individualized care. *Chest*. 2018;154:980–1.
 79. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev*. 2014;10:CD006322.
 80. Holland A, Ambrosino N. Pulmonary rehabilitation in restrictive thoracic disorders. In: Clini CE, Holland A, Pitta F, Troosters T, editors. *Textbook of pulmonary rehabilitation*. Springer pub.; 2017. p. 379–90.
 81. Raghu G, Rochweg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med*. 2015;192:e3–19.
 82. Ambrosino N, Fracchia C. The role of tele-medicine in patients with respiratory diseases. *Expert Rev Respir Med*. 2017;11:893–900.
 83. Widyastuti K, Makhahah DN, Setijadi AR, Sutanto YS, Suradi, Ambrosino N. Benefits and costs of home pedometer assisted physical activity in patients with COPD. A preliminary randomized controlled trial. *Pulmonology*. 2018;24:211–8.
 84. Bell EC, Cox NS, Goh N, Glaspole I, Westall GP, Watson A, et al. Oxygen therapy for interstitial lung disease: a systematic review. *Eur Respir Rev*. 2017;26:160080.
 85. Ambrosino N, Xie L. The Use of non-invasive ventilation during exercise training in COPD patients. *COPD*. 2017;14:396–400.
 86. Ambrosino N, Clini EM. Response to pulmonary rehabilitation: toward personalised programmes? *Eur Respir J*. 2015;46:1538–40.
 87. Vitacca M, Ambrosino N. Non invasive ventilation as an adjunct to exercise training in chronic ventilatory failure. A narrative review. *Respiration*. 2019;97:3–11.
 88. Dreher M, Ekkernkamp E, Schmoor C, Schoenheit-Kenn U, Wintekamp S, Kenn K. Pulmonary rehabilitation and noninvasive ventilation in patients with hypercapnic interstitial lung disease. *Respiration*. 2015;89:208–13.
 89. Jones S, Man WD, Gao W, Higginson IJ, Wilcock A, Maddocks M. Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. *Cochrane Database Syst Rev*. 2016;10:CD009419.
 90. Hill K, Cavalheri V, Mathur S, Roig M, Janaudis-Ferreira T, Robles P, et al. Neuromuscular electrostimulation for adults with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2018;5:CD010821.
 91. Lockett T, Phillips J, Johnson MJ, Farquhar M, Swan F, Assen T, Bhattarai P, Booth S. Contributions of a hand-held fan to self-management of chronic breathlessness. *Eur Respir J*. 2017;50, pii: 1700262.
 92. Lee AL, Dolmage TE, Rhim M, Goldstein RS, Brooks D. The impact of listening to music during a high-intensity exercise endurance test in people with COPD. *Chest*. 2018;153:1134–41.
 93. Bausewein C, Booth S, Gysels M, Higginson I. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. *Cochrane Database Syst Rev*. 2008;2:CD005623.
 94. Zeng YS, Wang C, Ward KE, Hume AL. Complementary and alternative medicine in hospice and palliative care: a systematic review. *J Pain Symptom Manage*. 2018;56:781–94.
 95. Lovell N, Etkind SN, Bajwah S, Maddocks M, Higginson IJ. Control and context are central for people with advanced illness experiencing breathlessness: a systematic review and thematic synthesis. *J Pain Symptom Manage*. 2019;57, 140–55.e2.
 96. Simon ST, Weingartner V, Higginson IJ, Benalia H, Gysels M, Murtagh FE, et al. ‘‘I can breathe again!’’ Patients’ self-management strategies for episodic breathlessness in advanced disease, derived from qualitative interviews. *J Pain Symptom Manage*. 2016;52:228–34.
 97. Brighton LJ, Miller S, Farquhar M, Booth S, Yi D, Gao W, et al. Holistic services for people with advanced disease and chronic breathlessness: a systematic review and meta-analysis. *Thorax*. 2018;29:270–81.
 98. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, 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;2:979–87.
 99. Kreuter M, Bendstrup E, Russell AM, Bajwah S, Lindell K, Adir Y, et al. Palliative care in interstitial lung disease: living well. *Lancet Respir Med*. 2017;5:968–80.
 100. Sorathia L. Palliative care in chronic obstructive pulmonary disease. *Med Clin North Am*. 2019;7. Available on line: <https://doi.org/10.1016/j.mcna.2018.12.010>
 101. Yoong J, Park ER, Greer JA, Jackson VA, Gallagher ER, Pirl WF, et al. Early palliative care in advanced lung cancer: a qualitative study. *JAMA Intern Med*. 2013;173:283–90.
 102. Sharp C, Lamb H, Jordan N, Edwards A, Gunary R, Meek P, et al. Development of tools to facilitate palliative and supportive care referral for patients with idiopathic pulmonary fibrosis. *BMJ Support Palliat Care*. 2018;8:340–6.
 103. Rush B, Hertz P, Bond A, McDermid RC, Celi LA. Use of palliative care in patients with end-stage COPD and receiving home oxygen: national trends and barriers to care in the United States. *Chest*. 2017;15:41–6.
 104. Qian MY, Politis J, Thompson M, Wong D, Le B, Irving L, et al. Individualized breathlessness interventions may improve outcomes in patients with advanced COPD. *Respirology*. 2018;23:1146–51.
 105. Jolly K, Sidhu MS, Hewitt CA, Coventry PA, Daley A, Jordan R, et al. Self management of patients with mild COPD in primary care: randomised controlled trial. *BMJ*. 2018;361: k2241.
 106. Troosters T, Maltais F, Leidy N, Lavoie KL, Sedeno M, Janssens W, et al. Effect of bronchodilation, exercise training, and behavior modification on symptoms and physical activity in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;198:1021–32.
 107. Steurer-Stey C, Dalla Lana K, Braun J, Ter Riet G, Puhan MA. Effects of the ‘‘Living well with COPD’’ intervention in primary care: a comparative study. *Eur Respir J*. 2018;51, pii: 1701375.