REVIEW ARTICLE

Chronic Obstructive Pulmonary Disease: Part III

An Overview of the Non- Pharmacological and Non-surgical Management of Chronic Obstructive Pulmonary Disease

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Abstract

Over the years, the management of chronic obstructive pulmonary disease has evolved, but given the high mortality and morbidity of COPD, much work still needs to be done. To date, none of the existing pharmacological therapies for COPD has been shown conclusively to modify the long-term decline in lung function. Several trials have been completed to evaluate options that can improve patient symptoms and quality of life.
Optimal management for patients with COPD requires both pharmacological and non-pharmacological managements. Some of the non-pharmacological options for the management of COPD like Oxygen therapy have proven reduction in mortality and mortality, and an improvement in the quality of life. Lung transplant is the only treatment that can stop the decline in lung function. Smoking cessation is the non-pharmacological intervention with the greatest capacity to influence the natural course of COPD. Pulmonary rehabilitation programs are evidence based, multidisciplinary and comprehensive interventions for patients with COPD. These programs involve patient assessment, exercise training, education, nutrition and psychosocial support. Pulmonary rehabilitation programs are designed to reduce symptoms, optimize functional status, increase participation and reduce health care cost through stabilizing or reversing systemic manifestations of the disease.
This article discusses the most used non pharmacological management of COPD and their usefulness in relieving symptoms and improving the quality of life for patients with severe COPD. These treatment options are used in addition to optimal pharmacological therapy.

Keywords: smoking cessation, rehabilitation, oxygen, Noninvasive mechanical ventilation, Palliative care

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease. It is amongst the fastest growing chronic diseases in the world today.[1] It is characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients with COPD.[2]

COPD is the third most common cause of death in the United States.[3] It is the fourth leading cause of death in the world and projected to get worse because of the continuous exposure to noxious particle, the aging world population, increasing smoking rates and decrease in other common causes of death like ischemic heart disease and infections.[2]

Symptoms of COPD could be debilitating, and lead to a very poor quality of life.

Pharmacological therapies are still considered the core of COPD management. In fact, pharmacological therapies absorb a substantial part of the resources used for long term management of COPD.[4] The cost of management of COPD increases during acute exacerbations and as severity of the disease gets worse.[5] Once a diagnosis of COPD is made, there is no intervention, except for a lung transplant, that will prevent the progression of the disease or decrease mortality.[2] Non pharmacological management is therefore promoted for symptom management, cost management, improvement of quality of life and in the case of transplant, change in the course of the disease.[6]

The most widely used non pharmacological therapy for COPD include: Oxygen therapy, Noninvasive Positive Pressure Ventilation (NPPV), Smoking cessation, Neuromuscular Electrical Stimulation (NES), Pulmonary Rehabilitation (PR) and nutrition counselling. Surgical management for COPD also plays a major role. In fact, the only curative management for COPD is surgical. COPD management requires a multidisciplinary team approach and combination of both optimal pharmacological management and non-pharmacological therapies.

Current guidelines include very few recommendations on the optimal non pharmacological management for patients with severe COPD but there are several studies on the non -pharmacological management of COPD.[7]

In this article, we have discussed the main non-pharmacological and non-surgical management options for COPD, the evidence-based indications for the different options. Surgical managements and pharmacological managements have been addressed in separate articles.

Smoking Cessation

Smoking is the largest risk factor for the development of COPD. The amount and duration of smoking contribute to disease severity. This makes smoking cessation a crucial intervention for patients with COPD who still smoke. This intervention is considered to have the most significant capacity to affect the progression of COPD.[2] Smoking cessation is the single most effective therapy for COPD. It is associated with a reduction in symptoms and improvement in health status.[8,9] Smoking cessation is the only therapy that has clearly demonstrated to improve both the rate of lung loss and survival among patients with mild to moderate COPD.[10] Patients at all levels of disease severity should be offered counseling regarding smoking cessation. Unlike pharmacological therapies for COPD, smoking cessation is very cost-effective even in large populations and over long periods of time.[11-14] Increase rates of smoking cessation are seen with implementation of behavioral

interventions such as individual, group, or telephone counseling when compared to less intense clinical interventions. Stead LF et al. completed a systematic review of more than 53 studies and 25,000 participants, assessing the efficacy of counseling interventions with pharmacological therapy. In this review, they found they found greater smoking cessation success with this combined approach.[15]

Smoking cessation can be approached in several ways ranging from counselling to pharmacological interventions or both. The U. S. Preventive Services Task Force recommends that clinicians ask all adult patients about tobacco use and provide behavioral and pharmacological interventions to support cessation.[16]

The USPSTF suggests a 5-A strategy as follows:

- Ask about tobacco use
- Advise to quit using clear personalized messages
- Assess willingness to quit
- Assist to quit
- Arrange follow-up and support

Nicotine Replacement Therapy and Pharmacological Therapy for Smoking Cessation

The superior strategy for smoking cessation includes counseling with nicotine replacement therapy (NRT) or other pharmacological therapy. Vaping was advertised as a nicotine replacement therapy, but it has turned out to be a recruiting tool for younger people who were nonsmokers.[17,18] This is because tobacco is a major product in some of the vaping /e-cigarette products. Tetrahydrocannabinol (THC), cannabinoid (CBD) oils, Vitamin E, and other flavoring substances and additives have been added to nicotine and promoted to non-smoking adolescents and young adults.[4-7] It is still unclear if e-cigarettes actually decrease the incidence of tobacco use. NRT tends to be more effective than placebo and can increase long-term rates of abstinence. There are multiple nicotine replacement agents; however, they are generally similar in effectiveness. NRT include: gum; transdermal patch; nasal spray; lozenge; sublingual tablet.

When there are no contraindications, the most commonly used medications other than nicotine replacement agents are varenicline and bupropion. Nortriptyline has also been shown to offer some benefits regarding enhanced potential of cessation. A 2013 systematic review of pharmacological interventions for smoking cessation assessed these therapies. They defined long-term abstinence as a period of at least 6 months.[19] NRT and bupropion were found to be superior to placebo. Varenicline was superior to placebo, a single NRT and to bupropion. Combination NRT and varenicline were equally effective. Using a combination of a long-acting NRT agent with a short-acting one (for example a patch + gum) appears to be more effective than using a single agent.[2]

As compared to other single agents, Varenicline is reportedly more effective at producing long-term abstinence. It is associated with potential significant behavioral side effects, and it carries an FDA black box warning due to a heightened risk of neuropsychiatric symptoms such ad dream disorder, agitation, depressed mood, or suicidal ideation. [20]

Pulmonary Rehabilitation

There has been a strong push towards the use of Pulmonary Rehabilitation (PR) knowing that physical activity is a strong predictor of all-cause mortality in COPD.[21] PR focuses on exercise endurance and strengthening to improve dyspnea and health related-quality of life (HR-QOL) in COPD patients. Supervised exercise training at least twice weekly is recommended. PR interventions should be individualized to maximize personal functional gains. [22]

PR is a complex interdisciplinary non-pharmacological program that varies in what they offer and in composition of staff.

PR must be individualized for optimal results. It must include an initial comprehensive patient assessment in order to determine the best focus for an individualized treatment plan going forward. The initial comprehensive patient assessment includes an assessment of disease severity, physiological limitations, functional limitations, and comorbidities in order to set patient-specific goals.[23]

Behavior change is necessary to facilitate physical functionality and reduce the psychological impact of COPD. The positive impacts on HR-QOL, functional exercise, and maximal exercise capacity have been well studied and thoroughly reviewed by McCarthy B et al. in a systematic review from the Cochrane Library.[24] The American Thoracic Society and the European Respiratory Society describe PR as a spectrum of intervention strategies that include patient assessments, exercise training, education, nutritional intervention, and psychosocial support all aimed at treating the many aspects of exertional dyspnea. The primary benefits of PR include improvements in health related quality of life (HRQoL), dyspnea, walk distance, and exercise tolerance.[25] Newer studies are showing the promise of PR in reducing the decline in lung function, something previously shown only with smoking cessation or appropriate drug treatment.[26] Not surprisingly the benefits of PR gradually taper off after a year, even with telephone-assisted maintenance interventions and repeat annual PR. The addition of oxygen during PR for hypoxic and non-hypoxic patients improves maximal exercise performance but does not improve health status or dyspnea. Additionally, despite the significant number of PR studies, there is no defined best practice regarding length of intervention. The current recommendations are to individualize PR to the patient based upon patient or practice-based factors. Pulmonary rehabilitation can be conducted at a range of sites.[27]

Traditional pulmonary rehabilitation with supervision is the standard of care for pulmonary rehabilitation. Hospital based pulmonary rehabilitation programs are very effective. Some studies [28-30] have shown that both community and home-based PR programs could be as effective as hospital-based programs, in so far as the frequency and intensity are equivalent. [31] Home based PR programs have also been shown to improve dyspnea in COPD patients.[32] Pulmonary rehabilitation may help reduce anxiety and depression symptoms, [33] but the benefits of rehabilitation tend to wane over time.

Table 1: Composition of an Interdisciplinary Pulmonary Rehabilitation Team

Pulmonary Rehabilitation Team
• Physicians • Nurses • Respiratory Therapists • Physiotherapists • Physical Therapists • Psychologists • Behavioral Specialists • Exercise Physiologists • Nutritionists • Occupational Therapists • Social Workers

Table 2: Components of pulmonary rehabilitation

Pulmonary Rehabilitation Modalities
• Comprehensive Patient Assessment • Endurance Trainings • Strength Training • Education (smoking cessation, adherence to pharmacological and non-pharmacological treatment) • Behavioral Change • Self-Directed Care Planning

In contrast to the length of PR, there has been consensus on the intensity of exercise during PR with high intensity endurance training showing benefits over moderate intensity training in skeletal muscle strength, respiratory muscle strength, endurance, and dyspnea.[34] A patient's ability to tolerate certain levels of intensity will vary by their baseline COPD severity. Patients who are not able to tolerate high-intensity exercise will still benefit from PR. That is why PR has to be individualized after thoroughly evaluating the patient. Interestingly, specifically emphasizing respiratory muscle training provides insignificant improvements in functional capacity or exercise capacity, so sessions that focus on upper and lower body strength and endurance training are much more preferred.[35] Knowing that the effects of PR taper off after a year's time, educational support and PR psycho-social feedback that encourage an active lifestyle and continued self-directed exercise outside of PR are needed to prevent the reversal of any improvements obtained in PR.

More recently, there has been an interest in studying the effects of PR after an acute exacerbation of COPD (AECOPD) knowing that there is a huge burden on the health-care systems due to admissions and readmissions. Roberts CM et al. showed that 34% of acute COPD patients discharged from the hospital following an exacerbation are readmitted with 3 months.[36]

More strikingly, up to 25% of patients after an acute exacerbation may not recover to baseline peak flow after an acute exacerbation.[37] The location of PR after AECOPD can vary and can be hospital inpatient (at the time of AECOPD), hospital outpatient, community, and at home and all locations have shown degrees of success, with the inpatient and hospital outpatient trending towards the best results but at unsurprisingly highest costs.

In COPD, exercise intolerance is a defining limitation and skeletal muscle dysfunction is a defining extra pulmonary manifestation.[38] Importantly, studies have suggested that the skeletal muscle dysfunction is correlated with exercise limitations which itself is correlated to physical activity limitations. Interestingly, skeletal muscle dysfunction itself is an independence predictor of mortality in COPD irrespective of the degree of air-flow disease.[39] More interestingly, it has been recently suggested that resistance training may offer several advantages over endurance training knowing that resistance training involves less dyspnea than endurance training. A meta-analysis by Wen-hua Liao et al. revealed that there were no significant differences between resistance training and endurance training in functional exercise capacity (6 minute walk distance, 6MWD) and maximal exercise capacity. [40] Given that resistance training is less limited by dyspnea, either resistance training alone or a combination of resistance and endurance trainings may prove to be the best modality in PR, but further studies are needed to fully clarify.

Discussion of Pulmonary Rehabilitation cannot be complete without mentioning its barriers, which are numerous. Most of the barriers to access to PR include availability, cost, time-commitment, poor prior patient experience, and provider lack of familiarity. One international review of PR programs showed that <=1.2% of patients with COPD have access to its services.[41] Additional studies on access, availability, and cost-analysis are warranted in order to address the access gap and ensure that PR as a recommended and essential treatment of COPD is actually provided.

PR should be offered to all symptomatic COPD patients with exertional dyspnea at baseline or who are having an acute exacerbation of COPD as a best practice intervention. Patients who are unable to ambulate or who have a critical illness such as unstable angina must be exempted from PR. It must be a multidisciplinary program that includes education, behavioral enhancements towards self-improvements, and physical exercise—specifically high-intensity resistance and endurance training. Studies support improvements in HRQoL, dyspnea, and exercise tolerance after PR with benefits lasting 12-18 months. Unfortunately, maintenance PR has not been shown to extend improvements. But, at a minimum, encouragement of self-directed physical activity should be maintained as it is well-known that inactivity and poor walking ability is correlated with a worse prognosis. These summary recommendations are consistent with a recent official statement from the American Association of Cardiovascular and Pulmonary Rehabilitation.[42]

Neuromuscular electrical stimulation

Transcutaneous neuromuscular electrical stimulation (NMES) of the ambulatory muscles has been studied and may serve as a replacement to exercise to improve muscle function in severely limited, severely ill COPD patients.[43] The advantage of a non-exercise modality is obvious for severe COPD patients, especially knowing that NMES can be utilized in the home. The study showed significant improvements in functional mobility, exercise capacity, depression, and overall quality of life (QoL)

in patients with COPD regardless of the severity of airflow obstruction. NMES utilizes low electrical current to specific muscles via a trans-cutaneous method resulting in involuntary muscle contractions of targeted muscles. Given the limited amount of literature on NMES and COPD, more studies are suggested.

Oxygen

Supplemental oxygen is a critical component of acute therapy in patients with COPD exacerbation. Excess supplemental oxygen can worsen hypercapnia, so administration of supplemental oxygen should target pulse oxygen saturation (SpO2) of 88 to 92 percent or an arterial oxygen tension (PaO2) of approximately 60 to 70 mmHg.[1,44,45] Patients with COPD exacerbation and hypoxemia usually do not require a high FiO2 to correct the hypoxemia. Whenever there is need for high FiO2 to correct hypoxemia, other causes of hypoxemia should be investigated.

Long term oxygen therapy (LTOT) administered continuously to hypoxemic COPD patients increases survival.[43,46] Other than the mortality benefits of LTOT, LTOT also improves quality of life, cardiovascular morbidity, depression, cognitive function, exercise capacity, and frequency of hospitalization.[46-51]

Indications for continuous long-term oxygen therapy (LTOT) for patients with chronic lung disease are any one of these conditions:

- Arterial oxygen tension (PaO2) less than or equal to 55 mmHg (7.32 kPa)
- A pulse oxygen saturation (SpO2) less than or equal to 88 percent
- PaO2 less than or equal to 59 mmHg (7.85 kPa)
- SpO2 less than or equal to 89 percent if there is evidence of cor pulmonale, right heart failure, or erythrocytosis (hematocrit >55 percent).

In addition to the internationally agreed indications for oxygen, oxygen has been prescribed in several other clinical settings including:

- During exercise, pulmonary rehabilitation, and nocturnal desaturation.
- In patients with a reduction of PaO2 to 55 mmHg or less, or of SpO2 to 88 percent or less during exercise.
- In patients who develop dyspnea and ventilatory abnormalities during exercise

Supplemental oxygen may permit greater exertion in these patients even if they do not significantly desaturate during exercise.[52]

Some studies have suggested that supplemental oxygen during training does little to enhance exercise tolerance although there is a small benefit in terms of shortness of breath. Patients with severe disabling shortness of breath may find symptomatic relief with supplemental oxygen.[53]

When prescribing LTOT, the source of supplemental oxygen (gas or liquid), method of delivery, duration of use, and flow rate at rest and during exercise and sleep should be clearly stated.

Oxygen supplementation during exercise induce dose-dependent improvement in endurance and symptom perception in non-hypoxaemic COPD patients.[54] Emtner et al. completed a trial of supplemental oxygen during cycle ergometry in patients with COPD and exercise-hypoxemia, and noted that oxygen administered during exercise enabled patients to tolerate higher training intensity and increased exercise tolerance.[55]

Supplemental oxygen may improve shortness of breath and so allowing for greater intensities of exercise training in symptoms limited patients.[56]

Lacasse et al. conducted a randomized trial of ambulatory oxygen in patients with oxygen dependent COPD and found out that patients with COPD for whom ambulatory oxygen was prescribed are very sedentary. In addition, it appeared that the ambulatory oxygen therapy did not increase activity. [57]

Cochrane data base systemic review conducted by Rams et al. did not find any substantial evidence to back up the prescription of portable oxygen for this group of patients.[58]

The exact role of oxygen as a rehabilitative adjunct remains to be delineated.[44] It is still unclear whether enhanced exercise performance during a brief test translates into a meaningful increase in the ability to perform the activities of daily living. Also the proportion of patients who show improvements in exercise performance during a test of hyperoxic exercise need to be appropriately evaluated by clinical trials.[53]

Sleep-related breathing disorders (SRBD) are common in patients with COPD occurring in approximately 40 percent of patients.[59] Patients who have nocturnal oxygen desaturation should be evaluated for sleep-disordered breathing. The management of nocturnal desaturation should be determined by the cause of the saturation.

The prescription of LTOT has rare adverse effect for patients with COPD if administered correctly.[60] Facial and upper airway burns are an infrequent complication of LTOT, but can be severe and potentially life-threatening.[61-64] Patients should not smoke while using supplemental oxygen.[64] Oxygen should be kept at least six feet (two meters) away from any open flame, or sources of sparks.

The 2020 Gold guidelines recommend High-flow nasal therapy (HFNT) as an alternative to standard oxygen therapy or noninvasive positive pressure ventilation for COPD patients with acute hypoxemic respiratory failure. HFNT involves nasal delivery of heated and humidified oxygen and air gas blends via special devices at rates up to 8 L/min in infants and up to 60 L/min in adults.[65] HFNT may be associated with decreased respiratory rate and effort, decreased work of breathing, improved gas exchange, improved lung volume, dynamic compliance, trans-pulmonary pressures and homogeneity.[2] All these benefits of HFNT may improve oxygenation and clinical outcomes in patients with acute respiratory failure.[66] HFNT has also been reported to improve oxygenation and ventilation, decreases hypercarbia and improve health-related quality of life in patients with stable hypercapnic COPD.[67-70]

There are concerns about potential toxicities in patients administered oxygen in high concentrations (above 50 percent) for extended time periods. Some possible hazards of hyperoxemia include absorptive atelectasis, increases oxidative stress, inflammation, and peripheral vasoconstriction that may limit oxygen transport to the cells. These concerns have not been supported clinically. Also no clear cut-off of oxygen concentration has been noted to cause severe oxygen toxicity.[71]

NIPPV

Noninvasive positive pressure ventilation (NPPV) refers to positive pressure ventilation delivered through a noninvasive interface like a nasal mask, facemask, or nasal plugs. The use of noninvasive ventilation in patients with COPD is beneficial in the acute setting, but chronic use of NPPV in patients with COPD is still controversial.

Indications for NPPV in the acute setting include: [(2)]

- Severe dyspnea with clinical signs of respiratory muscle fatigue
- Increased work of breathing
- Respiratory acidosis (arterial pH ≤7.35 and arterial tension of carbon dioxide [PaCO2] ≥45 mmHg [≥6 kPa]).

Several studies have shown that NPPV improves important clinical outcomes in patients having an acute exacerbation of COPD, complicated by hypercapnic acidosis.[72-76] A meta-analysis was completed on 758 patients by Rams et al. comparing standard therapy alone to NPPV

plus standard therapy in patients having a COPD exacerbation complicated by hypercapnia ($PaCO_2$ >45 mmHg). They noted that NPPV led to a decrease in mortality, intubation rate, treatment failure, hospital length of stay and complications related to treatment.[73] These studies also showed that patients with severe exacerbations of COPD respond better to NPPV than patients with mild COPD exacerbations.[73-77] NPPV is superior to medical therapy alone for the management of severe exacerbations of COPD. [78-81]

One-year mortality was reported to be lower in patients receiving NIPPV for exacerbations of COPD than patients receiving either optimal medical therapy alone or conventional mechanical ventilation. [80] COPD patients who develop respiratory failure should be placed on NPPV given its proven decrease in morbidity, mortality and, decreased need for mechanical ventilation. These benefits have been shown in the settings of a medicine ward, intensive care unit, and even in the emergency department.[82] Patients with advanced COPD who are not candidates for active resuscitation or admission to the intensive care unit may still benefit from NIPPV in the general ward with up to 60% hospital survival.[83] When NPPV is delivered by face mask, the risks associated with invasive ventilation like ventilation acquired pneumonia are eliminated.

NPPV is also effective in facilitating extubation in patients who were on mechanical ventilation for an acute exacerbation of COPD. Patients who are placed on NPPV after extubation have fewer re-intubations, fewer tracheostomies, shorter stays in the intensive care unit, increased survival in the intensive care unit, and fewer complications.[82] NPPV should therefore be considered in patients that required intubation for respiratory failure particularly in those who have failed traditional weaning.

NPPV has physiologic benefits. Diaz et al. measured respiratory mechanics after the initiation of NPPV, and found a decreased respiratory rate, an increased tidal volume, and increased minute ventilation.[84] They also noted that PaO2 tends to increase as PaCO2 decreases.

Chronic use of NPPV in stable patients with COPD is still very controversial. Struik et al. completed a prospective, multicenter, randomized, controlled clinical trial on NPPV for the treatment of severe stable chronic obstructive pulmonary disease. They found out that there was no improvement in survival, number of health-related quality of life, mood, and exercise tolerance in patients who were placed on NPPV as compare to patients who were on the standard treatment. Patients on NPPV however did show improvements in daytime PaCO2, and nocturnal transcutaneous PCO2 measurements.[85]

The use of NPPV like continuous positive airway pressure in patients with obstructive sleep apnea and COPD decreases the rates of pulmonary hypertension and nocturnal hypoxemia.[86] NPPV has been used during exercise training in COPD patients[87,88] and especially during pulmonary rehabilitation. NPPV increases minute ventilation despite reduced inspiratory effort during pulmonary rehabilitation.[89] With an increase in minute ventilation, NPPV unloads inspiratory muscles,[90,91] and prolongs exercise induced lactatemia,[92] leading to reduced shortness of breath on exertion and improving exercise tolerance.[89,93-99]

Adding NIPPV to exercise training in patients with stable hypercapnic COPD improves PCO2, FEV1, dyspnea scale and Health Related Quality of life (HRQoL).

NPPV can be used as an alternative to invasive ventilation for symptom relieve in patients with end stage COPD.[83,100,101] Nava et al. performed a survey on the patients in an intermediate respiratory care unit. This

survey revealed that one third of patients with poor life expectancy use NPPV.[102] A Society of Critical Care Medicine Palliative Noninvasive Positive Ventilation Task Force has concluded that NPPV should be applied only after careful discussion of the goals of care, with explicit parameters for success and failure, by experienced personnel, and in appropriate healthcare settings for patients and families who choose to forego endotracheal intubation.[103]

Contraindications to NPPV

- Respiratory arrest
- Hemodynamically unstable patients
- Impaired mental status
- High risk of aspiration
- Recent trauma, surgery or burns
- Stable patients with chronic hypercapnia

Nutrition

Nutritional screening is recommended in the assessment of COPD. Measurements of BMI and weight change can be used for screening. A weight loss of 10% in 6 months or 5% in a month is considered significant. Weight loss and loss in fat mass is primarily the result of a negative balance between dietary intake and energy expenditure, while muscle wasting is a consequence of an impaired balance between protein synthesis and protein breakdown. Eating habits and energy intake is of major importance in these patients, but nutritional therapy may only be effective if combined with exercise or other anabolic stimuli.[104,105]

Weight loss is an independent predictor of morbidity,[106,107] and mortality in patients with COPD,[108-111] and evidence suggest that weight gain can reverse this increased mortality risk.[110] The presence of cachexia indicates a poor outcome in terms of morbidity, HRQoL and mortality in patients with chronic COPD. Weight loss, loss in free fat mass (FFM), and low body mass index (BMI) have been associated with a much poorer outcome in COPD patients.[112] Depletion of FFM is a significant problem in hospitalized patients with severe COPD,[113] as well as in outpatients with moderate airflow obstruction.[114] The causes of weight loss in COPD are multifactorial. Weight loss is a result of caloric imbalance due to increased energy demand and/or reduced dietary intake. This is a common and serious problem for patients with COPD.[108] Accelerated muscle proteolysis is considered the primary cause of the loss of lean body mass, not only in COPD, but also in many other chronic diseases.[115] Most studies of energy intake in COPD patients are supplementation studies and few are available in which the relationship between exacerbations, habitual energy intake and different classes of body mass index (BMI) are examined. Caloric imbalance and weight loss could be a result of eating difficulties,[111,116] higher metabolic rate, cost of ventilation,[106] and systemic inflammation caused by oxidative stress.[117,118]

Systematic analyses of dietary intake in COPD patients are scarce. Schols et al. reported an inadequate dietary intake for energy expenditure, especially in the more disabled COPD population.[104]

Studies suggest there may be some benefit to nutritional supplementation for malnourished COPD patients. One systematic review evaluating the use of nutritional supplementation in stable COPD patients, as measured by weight gain and increase in exercise capacity, found evidence of moderate-quality to support this approach.[119] In malnourished patients with COPD, nutritional supplementation promotes significant weight gain and leads to significant improvements in respiratory muscle strength and overall health-related quality of life.[120] Nutritional antioxidant supplementation (vitamin C and E, zinc, and selenium) has been shown to improve

antioxidant deficits, quadriceps strength, and serum total protein, without further improvement in quadriceps endurance. Only in malnourished patients has nutritional supplementation demonstrated significant improvements for 6-minute walk test, respiratory muscle strength and health status.[121] A 12-month nutritional intervention in muscle wasted patients had no effect on physical capacity but physical activity was significantly higher.[2]

Immunizations

Although influenza vaccine can reduce serious illness and death by about 50% in patients with COPD, only 62% of physicians administer influenza vaccination annually to their patients with moderate COPD and 71% to patients with severe COPD. Reported immunization rates against pneumococcal infections are 29% and 47% for patients with moderate and severe COPD, respectively.[122] COPD patients should receive the annual influenza vaccine, for improvement in morbidity and mortality. Additionally, the pneumococcal polysaccharide vaccination is recommended for COPD patients ages 65 and older, and for younger patients who have significant comorbid diseases.[123] Physicians should be more aware of vaccination and recommend both influenza and pneumococcal vaccines to all patients with COPD to reduce exacerbations.[124] A systematic review to evaluate current evidence on the immunogenicity, safety, efficacy, and effectiveness of seasonal influenza vaccination in patients with COPD conducted by Bekkat-Berkani R et al. found that the evidence supports seasonal influenza vaccination in patients with COPD as per current vaccination recommendations.[125]

Education and self-management and integrative care

So far there is no clear definition self-management the components of self-management and fidelity measures. The process requires iterative interactions between patients and healthcare professionals who are competent in delivering self-management interventions. In a randomized controlled study conducted by Benzo and McEvoy, health coaching delivered by a respiratory therapist or nurse may improve self-management abilities as demonstrated by meaningful improvements in Chronic Respiratory Disease Questionnaire mastery scores.[126] Clearly defining self-management interventions specifics, patient populations, follow-up times and outcome measures are pivotal for self-management. It is also challenging to formulate clear recommendations regarding the most effective form and content of a self-management intervention in COPD given the range of heterogeneity across studies. [2]

Psychosocial Support

Management of COPD can include interventions for depression, anxiety, or other emotional stress related to living with chronic lung disease. Healthcare providers should ensure that patients are educated in self-management skills and decision-making during COPD exacerbations. Discussions regarding advanced directives and end-of-life issues should also be facilitated during exacerbations. These are amongst the subject areas recommended for patient education programs by the GOLD guidelines.[2]

Pulmonary Rehabilitation programs, if available, often include psychosocial support aimed at offering coping strategies through encouragement of adaptive thoughts and behaviors.[127] Additionally, when appropriate, patients may benefit from referral to mental health providers for more specific therapeutic interventions aimed at helping them cope with the disease.

A philosophy that includes palliation of symptoms over the course of this disease, alongside disease-modifying therapies,

should be considered strongly rather than consideration of palliative care as an end-of life-measure.[128] Therefore, patients may benefit significantly from early referral to Palliative Care specialists, particularly when it is perceived that their disease state and symptoms are limiting their quality of life.

Palliative Care

Patients with COPD that are appropriate for palliative care (PC) will note that both PR and PC have similarities (Table 3). Both managements require multidisciplinary teams that focus on specific individual needs regarding relief of symptoms, improvements in functional status, and improvements in quality of life. The aim is to administer the right treatment to the right patient at the right time. The similarities of PC and PR go beyond their primary focuses: PC, similarly to PR, has been shown to improve some COPD patient metrics and thus there is an overlap in the two treatment modalities.

Table 3: Pulmonary rehabilitation vs Palliative care

	Pulmonary Rehabilitation	Palliative Care
Stage of Disease Targeted	All stages	All states
Aims	Reduce distressing symptoms, improve functional status, and enhance quality of life	Reduce distressing symptoms, improve functional status, and enhance quality of life
Style	Individualized	Individualized
Primary Focus	Raising functional status	Symptom relief
Care Team	Multi-disciplinary	Multi-disciplinary

Studies have shown that there are challenges in determining the prognosis and final course of advanced COPD,[129]therefor predicting survival in the disease is of great importance. Dajczman et al. showed that the 6MWT can be used to predict a high mortality. They predicted a high mortality rate in patients with severe COPD and a low 6MWT. They also suggested that those unable to achieve improvements in the 6MWT after PR may have the very worst prognosis.[130]

Given the challenges of determining an accurate diagnosis in COPD patients, PC should be offered to all chronic severe COPD patients who remain symptomatic and have functional limitations. The application of PC in COPD can be at any stage: acute, chronic, or terminal.[131] Other recommended triggers to use to prompt PC initiation or intensification are listed in (Table 4)

Table 4: Triggers prompting the Palliative care

Triggers Prompting Palliative Care Initiation or Intensification.[131]
Multiple Hospitalizations
Decline in Functional Status (ADLs)
Disabling Dyspnea
FEV1 < 30%
Oxygen Saturation < 88%
PCO2 > 50mm
Resting Tachycardia > 100 beats/min
Uncompensated Cor Pulmonale

Additionally, an affirmative to the "surprise question" of would the provider be surprised if her or his COPD patient died in the next year may be another indicator for PC consultation or intensification. This question has been shown to identify patients with poor prognoses in cancer patients,[133] and it may be helpful in other diagnoses. Clearly, studying the application of this question in COPD patients would need to take place for a definitive answer.

The primary symptoms of COPD patients targeted by PC are fatigue, cough, dry mouth, pain, refractory breathlessness, anxiety, depression, and decreased quality of life. To complicate PC for the COPD patient, his or her symptoms of cough, dry mouth, and breathlessness cause communication difficulties for the patient so the healthcare team must be vigilant in recognizing the need to act towards symptom relief. It has been shown, unfortunately, that COPD patients receive less palliative care and more aggressive care compared to those, say, with lung cancer.[132] Some of the specific treatments recommended for COPD patients requiring PC are pharmacological therapy (including opioids), physical rehabilitation, oxygen therapy, and noninvasive ventilation for dyspnea and breathlessness and, in turn, using physical rehabilitation and pharmacological therapy (including sedation) for anxiety and depression.[2,133]

Due to the challenges in predicting mortality in COPD along with the communication challenges in COPD patients, PC services have been historically underutilized in patients with COPD. Recommendations are to move towards an earlier and more proactive palliative care plan for COPD patients targeting the use of Palliative Care Services more similarly to Pulmonary Rehabilitation Services in this group.

Conclusion

Severe COPD accounts for one of the highest causes of death and has a very high clinical and cost burden. COPD has poor prognosis and the highest cost is spent on pharmacological management. Current Pharmacological managements are unable to cure COPD. Non-pharmacological treatment is complementary to pharmacological treatment and should form part of the comprehensive management of COPD. Non pharmacological management provides significant benefits to patients with severe COPD who are symptomatic despite being on optimal medical therapy. The main goals of non-pharmacological therapy are to relieve symptoms, improve health related quality of life and slow down disease progression. The only curative management for COPD is lung transplant, but it comes with high risks. This article discusses the main non pharmacological/ non-surgical management of severe COPD. The multidisciplinary approach to the management of stable severe

COPD and COPD exacerbation ranging from management in the medicine floor setting, intensive care setting and the palliative care approach to these patients. Future directions are needed from the governing bodies of COPD as to the indications and most appropriate use of the non-pharmacological management of COPD.

References

1. Akwe, Joyce and Fair, Nadene, Chronic Obstructive Pulmonary Disease: An Overview of Epidemiology, Pathophysiology, Diagnosis, Staging and Management (March 31, 2016). International Journal of Clinical and Experimental Medical Sciences, 2016; 2(2): 13-25. Available at SSRN: https://ssrn.com/abstract=2765281 2(2): 13-25. Available at SSRN: http://ssrn.com/abstract=2765281. In: Fair, ed2016.
2. Gold Reports 2020 - Global Initiative for Chronic Obstructive Pulmonary Disease PDF. The GOLD 2020 report is a revision of the GOLD 2019 report. ... What is (and what is not) a COPD exacerbation: thoughts from the new GOLD guidelines. Goldcopd.org › 2019/11 › GOLD-2020-REPORT-ver1.0wms.pdf https://goldcopd.org. Published 2019/11.
3. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(10):1005-1012.
4. Friedman M, Hilleman DE. Economic burden of chronic obstructive pulmonary disease. Impact of new treatment options. *Pharmacoeconomics.* 2001;19(3):245-254.
5. Miratvilles M, Murio C,Guerrero T, Gisbert R, on behalf of the DAFNE Study Group. Cost of chronic bronchitis and COPD. A 1-year follow-up study. Chest.2003; 123:784–791. 2003.
6. Faulkner MA, Hilleman DE. The economic impact of chronic obstructive pulmonary disease. *Expert Opin Pharmacother.* 2002;3(3):219-228.
7. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2007;176(6):532-555.
8. Calverley PM. Reducing the frequency and severity of exacerbations of chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* 2004;1(2):121-124.
9. Kanner RE, Connett JE, Williams DE, Buist AS. Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: the Lung Health Study. *Am J Med.* 1999;106(4):410-416.
10. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med.* 2005;142(4):233-239.
11. Faulkner MA, Lenz TL, Stading JA. Cost-effectiveness of smoking cessation and the implications for COPD. *Int J Chron Obstruct Pulmon Dis.* 2006;1(3):279-287.
12. Hoogendoorn M, Welsing P, Rutten-van Molken MP. Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. *Curr Med Res Opin.* 2008;24(1):51-61.
13. 1. Johansson PM TP, Guldbrandsson KA,, LA. L. 1. Johansson PM, Tillgren PE, Guldbrandsson KA, Lindholm LA. A model for cost-effectiveness analyses of smoking cessation interventions applied to a Quit-and-Win contest for mothers of small children. Scand J Public Health. 2005;33:343–52. 2005.
14. J. T. Tsevat J. Impact and cost-effectiveness of smoking interventions. Am J Med. 1992;93:43S–7S. 1992.
15. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for

smoking cessation. *Cochrane Database Syst Rev*. 2016;3:Cd008286.
16. USPSTF. U.S. Preventive Services Task Force. Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions. September 2015. http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions. Published 2015. Accessed.
17. Hajek P, Etter JF, Benowitz N, Eissenberg T, McRobbie H. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. *Addiction*. 2014;109(11):1801-1810.
18. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*. 2013;382(9905):1629-1637.
19. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013(5):Cd009329.
20. Hays JT, McFadden DD, Ebbert JO. Pharmacologic agents for tobacco dependence treatment: 2011 update. *Curr Atheroscler Rep*. 2012;14(1):85-92.
21. Waschki B, Kirsten A, Holz O, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest*. 2011;140(2):331-342.
22. Alison JA, McKeough ZJ, Johnston K, et al. Australian and New Zealand Pulmonary Rehabilitation Guidelines. *Respirology*. 2017;22(4):800-819.
23. Nici L, Raskin J, Rochester CL, et al. Pulmonary rehabilitation: WHAT WE KNOW AND WHAT WE NEED TO KNOW. *J Cardiopulm Rehabil Prev*. 2009;29(3):141-151.
24. 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.
25. Mulhall P, Criner G. Non-pharmacological treatments for COPD. *Respirology*. 2016;21(5):791-809.
26. Incorvaia C, Russo A, Foresi A, et al. Effects of pulmonary rehabilitation on lung function in chronic obstructive pulmonary disease: the FIRST study. *Eur J Phys Rehabil Med*. 2014;50(4):419-426.
27. Spruit MA. Pulmonary rehabilitation. *Eur Respir Rev*. 2014;23(131):55-63.
28. Holland AE, Mahal A, Hill CJ, et al. Home-based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial. *Thorax*. 2017;72(1):57-65.
29. Holland AE, Cox NS. Telerehabilitation for COPD: Could pulmonary rehabilitation deliver on its promise? *Respirology*. 2017;22(4):626-627.
30. Maltais F, Bourbeau J, Shapiro S, et al. Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*. 2008;149(12):869-878.
31. Bourne S, DeVos R, North M, et al. Online versus face-to-face pulmonary rehabilitation for patients with chronic obstructive pulmonary disease: randomised controlled trial. *BMJ Open*. 2017;7(7):e014580.
32. Horton EJ, Mitchell KE, Johnson-Warrington V, et al. Comparison of a structured home-based rehabilitation programme with conventional supervised pulmonary rehabilitation: a randomised non-inferiority trial. *Thorax*. 2018;73(1):29-36.
33. Gordon CS, Waller JW, Cook RM, Cavalera SL, Lim WT, Osadnik CR.

Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis. *Chest.* 2019;156(1):80-91.
34. Gimenez M, Servera E, Vergara P, Bach JR, Polu JM. Endurance training in patients with chronic obstructive pulmonary disease: a comparison of high versus moderate intensity. *Arch Phys Med Rehabil.* 2000;81(1):102-109.
35. Lotters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. *Eur Respir J.* 2002;20(3):570-576.
36. Roberts CM, Lowe D, Bucknall CE, Ryland I, Kelly Y, Pearson MG. Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. *Thorax.* 2002;57(2):137-141.
37. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2000;161(5):1608-1613.
38. Agusti A. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). *Proc Am Thorac Soc.* 2007;4(7):522-525.
39. Swallow EB, Reyes D, Hopkinson NS, et al. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax.* 2007;62(2):115-120.
40. Soler X, Gaio E, Powell FL, et al. High Prevalence of Obstructive Sleep Apnea in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc.* 2015;12(8):1219-1225.
41. Desveaux L, Janaudis-Ferreira T, Goldstein R, Brooks D. An international comparison of pulmonary rehabilitation: a systematic review. *Copd.* 2015;12(2):144-153.
42. Garvey C, Bayles MP, Hamm LF, et al. Pulmonary Rehabilitation Exercise Prescription in Chronic Obstructive Pulmonary Disease: Review of Selected Guidelines: AN OFFICIAL STATEMENT FROM THE AMERICAN ASSOCIATION OF CARDIOVASCULAR AND PULMONARY REHABILITATION. *J Cardiopulm Rehabil Prev.* 2016;36(2):75-83.
43. Coquart JB, Grosbois JM, Olivier C, Bart F, Castres I, Wallaert B. Home-based neuromuscular electrical stimulation improves exercise tolerance and health-related quality of life in patients with COPD. *Int J Chron Obstruct Pulmon Dis.* 2016;11:1189-1197.
44. Stoller JK, Panos RJ, Krachman S, Doherty DE, Make B. Oxygen therapy for patients with COPD: current evidence and the long-term oxygen treatment trial. *Chest.* 2010;138(1):179-187.
45. Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *Bmj.* 2010;341:c5462.
46. Tarpy SP, Celli BR. Long-term oxygen therapy. *N Engl J Med.* 1995;333(11):710-714.
47. Eaton T, Lewis C, Young P, Kennedy Y, Garrett JE, Kolbe J. Long-term oxygen therapy improves health-related quality of life. *Respir Med.* 2004;98(4):285-293.
48. Okubadejo AA, Paul EA, Jones PW, Wedzicha JA. Does long-term oxygen therapy affect quality of life in patients with chronic obstructive pulmonary disease and severe hypoxaemia? *Eur Respir J.* 1996;9(11):2335-2339.

49. Ringbaek TJ, Viskum K, Lange P. Does long-term oxygen therapy reduce hospitalisation in hypoxaemic chronic obstructive pulmonary disease? *Eur Respir J.* 2002;20(1):38-42.
50. Haidl P, Clement C, Wiese C, Dellweg D, Kohler D. Long-term oxygen therapy stops the natural decline of endurance in COPD patients with reversible hypercapnia. *Respiration.* 2004;71(4):342-347.
51. Tanni SE, Vale SA, Lopes PS, Guiotoko MM, Godoy I. Influence of the oxygen delivery system on the quality of life of patients with chronic hypoxemia. *J Bras Pneumol.* 2007;33(2):161-167.
52. Yamamoto H, Teramoto S, Yamaguchi Y, et al. Long-term oxygen administration reduces plasma adrenomedullin levels in patients with obstructive sleep apnea syndrome. *Sleep Med.* 2007;9(1):80-87.
53. Snider GL. Enhancement of exercise performance in COPD patients by hyperoxia: a call for research. *Chest.* 2002;122(5):1830-1836.
54. Somfay A, Porszasz J, Lee SM, Casaburi R. Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxaemic COPD patients. *Eur Respir J.* 2001;18(1):77-84.
55. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. *Am J Respir Crit Care Med.* 2003;168(9):1034-1042.
56. O'Donnell DE, D'Arsigny C, Webb KA. Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;163(4):892-898.
57. Lacasse Y, Lecours R, Pelletier C, Begin R, Maltais F. Randomised trial of ambulatory oxygen in oxygen-dependent COPD. *Eur Respir J.* 2005;25(6):1032-1038.
58. Ram FS, Wedzicha JA. Ambulatory oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2002(2):Cd000238.
59. Budhiraja R, Siddiqi TA, Quan SF. Sleep disorders in chronic obstructive pulmonary disease: etiology, impact, and management. *J Clin Sleep Med.* 2015;11(3):259-270.
60. Croxton TL, Bailey WC. Long-term oxygen treatment in chronic obstructive pulmonary disease: recommendations for future research: an NHLBI workshop report. *Am J Respir Crit Care Med.* 2006;174(4):373-378.
61. Amani H, Lozano DD, Blome-Eberwein S. Brother, have you got a light? Assessing the need for intubation in patients sustaining burn injury secondary to home oxygen therapy. *J Burn Care Res.* 2012;33(6):e280-285.
62. Murabit A, Tredget EE. Review of burn injuries secondary to home oxygen. *J Burn Care Res.* 2012;33(2):212-217.
63. Sharma G, Meena R, Goodwin JS, Zhang W, Kuo YF, Duarte AG. Burn injury associated with home oxygen use in patients with chronic obstructive pulmonary disease. *Mayo Clin Proc.* 2015;90(4):492-499.
64. Carlos WG, Baker MS, McPherson KA, Bosslet GT, Sood R, Torke AM. Smoking-Related Home Oxygen Burn Injuries: Continued Cause for Alarm. *Respiration.* 2016;91(2):151-155.
65. Roca O, Hernandez G, Diaz-Lobato S, Carratala JM, Gutierrez RM, Masclans JR. Current evidence for the effectiveness of heated and humidified high flow nasal cannula supportive therapy in adult patients with respiratory failure. *Crit Care.* 2016;20(1):109.
66. Mauri T, Turrini C, Eronia N, et al. Physiologic Effects of High-Flow Nasal

Cannula in Acute Hypoxemic Respiratory Failure. *Am J Respir Crit Care Med.* 2017;195(9):1207-1215.
67. Frat JP, Coudroy R, Marjanovic N, Thille AW. High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure. *Ann Transl Med.* 2017;5(14):297.
68. Nagata K, Kikuchi T, Horie 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(4):432-439.
69. Braunlich J, Dellweg D, Bastian A, et al. Nasal high-flow versus noninvasive ventilation in patients with chronic hypercapnic COPD. *Int J Chron Obstruct Pulmon Dis.* 2019;14:1411-1421.
70. Bruni A, Garofalo E, Cammarota G, et al. High Flow Through Nasal Cannula in Stable and Exacerbated Chronic Obstructive Pulmonary Disease Patients. *Rev Recent Clin Trials.* 2019;14(4):247-260.
71. Sjoberg F, Singer M. The medical use of oxygen: a time for critical reappraisal. *J Intern Med.* 2013;274(6):505-528.
72. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med.* 1995;333(13):817-822.
73. Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2004(1):Cd004104.
74. Keenan SP, Sinuff T, Cook DJ, Hill NS. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. *Ann Intern Med.* 2003;138(11):861-870.
75. Williams JW, Jr., Cox CE, Hargett CW, et al. AHRQ Comparative Effectiveness Reviews. In: *Noninvasive Positive-Pressure Ventilation (NPPV) for Acute Respiratory Failure.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.
76. Lindenauer PK, Stefan MS, Shieh MS, Pekow PS, Rothberg MB, Hill NS. Outcomes associated with invasive and noninvasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease. *JAMA Intern Med.* 2014;174(12):1982-1993.
77. Keenan SP, Powers CE, McCormack DG. Noninvasive positive-pressure ventilation in patients with milder chronic obstructive pulmonary disease exacerbations: a randomized controlled trial. *Respir Care.* 2005;50(5):610-616.
78. Martin TJ, Hovis JD, Costantino JP, et al. A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. *Am J Respir Crit Care Med.* 2000;161(3 Pt 1):807-813.
79. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet.* 2000;355(9219):1931-1935.
80. Conti G, Antonelli M, Navalesi P, et al. Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. *Intensive Care Med.* 2002;28(12):1701-1707.
81. Kwok H, McCormack J, Cece R, Houtchens J, Hill NS. Controlled trial of oronasal versus nasal mask ventilation in

the treatment of acute respiratory failure. *Crit Care Med.* 2003;31(2):468-473.
82. Safka KA, McIvor RA. Non-pharmacological management of chronic obstructive pulmonary disease. *Ulster Med J.* 2015;84(1):13-21.
83. Schettino G, Altobelli N, Kacmarek RM. Noninvasive positive pressure ventilation reverses acute respiratory failure in select "do-not-intubate" patients. *Crit Care Med.* 2005;33(9):1976-1982.
84. Diaz O, Iglesia R, Ferrer M, et al. Effects of noninvasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1997;156(6):1840-1845.
85. 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(9):826-834.
86. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med.* 2010;182(3):325-331.
87. Ambrosino N, Strambi S. New strategies to improve exercise tolerance in chronic obstructive pulmonary disease. *Eur Respir J.* 2004;24(2):313-322.
88. Ambrosino N. Assisted ventilation as an aid to exercise training: a mechanical doping? In: *Eur Respir J.* Vol 27. England2006:3-5.
89. Maltais F, Reissmann H, Gottfried SB. Pressure support reduces inspiratory effort and dyspnea during exercise in chronic airflow obstruction. *Am J Respir Crit Care Med.* 1995;151(4):1027-1033.
90. Polkey MI, Kyroussis D, Mills GH, et al. Inspiratory pressure support reduces slowing of inspiratory muscle relaxation rate during exhaustive treadmill walking in severe COPD. *Am J Respir Crit Care Med.* 1996;154(4 Pt 1):1146-1150.
91. Kyroussis D, Polkey MI, Hamnegard CH, Mills GH, Green M, Moxham J. Respiratory muscle activity in patients with COPD walking to exhaustion with and without pressure support. *Eur Respir J.* 2000;15(4):649-655.
92. Polkey MI, Hawkins P, Kyroussis D, Ellum SG, Sherwood R, Moxham J. Inspiratory pressure support prolongs exercise induced lactataemia in severe COPD. *Thorax.* 2000;55(7):547-549.
93. Keilty SE, Ponte J, Fleming TA, Moxham J. Effect of inspiratory pressure support on exercise tolerance and breathlessness in patients with severe stable chronic obstructive pulmonary disease. *Thorax.* 1994;49(10):990-994.
94. Bianchi L, Foglio K, Pagani M, Vitacca M, Rossi A, Ambrosino N. Effects of proportional assist ventilation on exercise tolerance in COPD patients with chronic hypercapnia. *Eur Respir J.* 1998;11(2):422-427.
95. Johnson JE, Gavin DJ, Adams-Dramiga S. Effects of training with heliox and noninvasive positive pressure ventilation on exercise ability in patients with severe COPD. *Chest.* 2002;122(2):464-472.
96. van 't Hul A, Kwakkel G, Gosselink R. The acute effects of noninvasive ventilatory support during exercise on exercise endurance and dyspnea in patients with chronic obstructive pulmonary disease: a systematic review. *J Cardiopulm Rehabil.* 2002;22(4):290-297.
97. Costes F, Agresti A, Court-Fortune I, Roche F, Vergnon JM, Barthelemy JC. Noninvasive ventilation during exercise training improves exercise tolerance in

patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil.* 2003;23(4):307-313.
98. van 't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G. Training with inspiratory pressure support in patients with severe COPD. *Eur Respir J.* 2006;27(1):65-72.
99. van 't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G. Acute effects of inspiratory pressure support during exercise in patients with COPD. *Eur Respir J.* 2004;23(1):34-40.
100. Levy M, Tanios MA, Nelson D, et al. Outcomes of patients with do-not-intubate orders treated with noninvasive ventilation. *Crit Care Med.* 2004;32(10):2002-2007.
101. Chu CM, Chan VL, Wong IW, Leung WS, Lin AW, Cheung KF. Noninvasive ventilation in patients with acute hypercapnic exacerbation of chronic obstructive pulmonary disease who refused endotracheal intubation. *Crit Care Med.* 2004;32(2):372-377.
102. Nava S, Sturani C, Harti S, et al. End-of-life decision-making in respiratory intermediate units: A european survey. *Rev Port Pneumol.* 2007;13(6):883-887.
103. Curtis JR, Cook DJ, Sinuff T, et al. Noninvasive positive pressure ventilation in critical and palliative care settings: understanding the goals of therapy. *Crit Care Med.* 2007;35(3):932-939.
104. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. *Am J Respir Crit Care Med.* 1995;152(4 Pt 1):1268-1274.
105. Creutzberg EC, Wouters EF, Mostert R, Weling-Scheepers CA, Schols AM. Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. *Nutrition.* 2003;19(2):120-127.
106. Schols AM, Creutzberg EC, Buurman WA, Campfield LA, Saris WH, Wouters EF. Plasma leptin is related to proinflammatory status and dietary intake in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1999;160(4):1220-1226.
107. Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J.* 1994;7(10):1793-1797.
108. Wouters EF. Nutrition and metabolism in COPD. *Chest.* 2000;117(5 Suppl 1):274s-280s.
109. Pouw EM, Ten Velde GP, Croonen BH, Kester AD, Schols AM, Wouters EF. Early non-elective readmission for chronic obstructive pulmonary disease is associated with weight loss. *Clin Nutr.* 2000;19(2):95-99.
110. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1999;160(6):1856-1861.
111. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1998;157(6 Pt 1):1791-1797.
112. Guo Y, Zhang T, Wang Z, et al. Body mass index and mortality in chronic obstructive pulmonary disease: A dose-response meta-analysis. *Medicine (Baltimore).* 2016;95(28):e4225.
113. Gray-Donald K, Gibbons L, Shapiro SH, Macklem PT, Martin JG. Nutritional status and mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1996;153(3):961-966.

114. Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J.* 2003;21(2):347-360.
115. Engelen MP, Schols AM, Lamers RJ, Wouters EF. Different patterns of chronic tissue wasting among patients with chronic obstructive pulmonary disease. *Clin Nutr.* 1999;18(5):275-280.
116. Nicklas BJ, Tomoyasu N, Muir J, Goldberg AP. Effects of cigarette smoking and its cessation on body weight and plasma leptin levels. *Metabolism.* 1999;48(6):804-808.
117. Palange P, Forte S, Felli A, Galassetti P, Serra P, Carlone S. Nutritional state and exercise tolerance in patients with COPD. *Chest.* 1995;107(5):1206-1212.
118. MacNee W. Oxidative stress and lung inflammation in airways disease. *Eur J Pharmacol.* 2001;429(1-3):195-207.
119. Ferreira RM, de Souza ESNA, Salis LHA, et al. Troponin I elevation and all-cause mortality after elective percutaneous coronary interventions. *Cardiovasc Revasc Med.* 2017;18(4):255-260.
120. Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2012;12:Cd000998.
121. Gouzi F, Maury J, Heraud N, et al. Additional Effects of Nutritional Antioxidant Supplementation on Peripheral Muscle during Pulmonary Rehabilitation in COPD Patients: A Randomized Controlled Trial. *Oxid Med Cell Longev.* 2019;2019:5496346.
122. Rutschmann OT, Janssens JP, Vermeulen B, Sarasin FP. Knowledge of guidelines for the management of COPD: a survey of primary care physicians. *Respir Med.* 2004;98(10):932-937.
123. Kim DK, Bridges CB, Harriman KH. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older: United States, 2016. *Ann Intern Med.* 2016;164(3):184-194.
124. Cimen P, Unlu M, Kirakli C, et al. Should Patients With COPD Be Vaccinated? *Respir Care.* 2015;60(2):239-243.
125. Bekkat-Berkani R, Wilkinson T, Buchy P, et al. Seasonal influenza vaccination in patients with COPD: a systematic literature review. *BMC Pulm Med.* 2017;17(1):79.
126. Benzo R, McEvoy C. Effect of Health Coaching Delivered by a Respiratory Therapist or Nurse on Self-Management Abilities in Severe COPD: Analysis of a Large Randomized Study. *Respir Care.* 2019;64(9):1065-1072.
127. Corhay JL, Moermans C, Henket M, Nguyen Dang D, Duysinx B, Louis R. Increased of exhaled breath condensate neutrophil chemotaxis in acute exacerbation of COPD. *Respir Res.* 2014;15:115.
128. Lilly EJ, Senderovich H. Palliative care in chronic obstructive pulmonary disease. *J Crit Care.* 2016;35:150-154.
129. Pinnock H, Kendall M, Murray SA, et al. Living and dying with severe chronic obstructive pulmonary disease: multi-perspective longitudinal qualitative study. *Bmj.* 2011;342:d142.
130. Dajczman E, Wardini R, Kasymjanova G, Prefontaine D, Baltzan MA, Wolkove N. Six minute walk distance is a predictor of survival in patients with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. *Can Respir J.* 2015;22(4):225-229.
131. Reticker AL, Nici L, ZuWallack R. Pulmonary rehabilitation and palliative care in COPD: Two sides of the same coin? *Chron Respir Dis.* 2012;9(2):107-116.

132. Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax.* 2000;55(12):1000-1006.

133. Carlucci A, Guerrieri A, Nava S. Palliative care in COPD patients: is it only an end-of-life issue? *Eur Respir Rev.* 2012;21(126):347-354.

