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A Review of the Non Pharmacologic 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 of COPD requires both pharmacologic and non-pharmacologic interventions. Some of the non-pharmacologic 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-pharmacologic 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 pharmacologic 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 pharmacologic therapy.

Keywords: Smoking Cessation, Pulmonary Rehabilitation, Oxygen, Noninvasive Mechanical Ventilation, Lung Surgical Intervention

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease. It is among the fastest growing chronic diseases diagnosed 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 lungs to noxious particles or gases.

Exacerbations and comorbidities contribute to the overall severity in individual patients. [2] COPD is reported as the sixth most common cause of death today, but it is predicted to be the third most common cause of death in 2020 due to increasing smoking rates and a decrease in other common causes of death such as ischemic heart disease and infections. [1]

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

Pharmacologic therapy is still considered the core of COPD management. In fact, pharmacologic therapy absorbs a substantial part of the resources used for long term management of COPD. [3] The cost increases during acute exacerbations and as severity of the disease progresses. [4] Once a diagnosis of COPD is made, there is no intervention, except for lung transplant, that will prevent the progression of the disease or decrease mortality. [2] Non pharmacologic 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. [5] The most widely used non pharmacologic therapies for COPD include: oxygen therapy, noninvasive positive pressure ventilation (NPPV), smoking cessation,

neuromuscular electrical stimulation (NMES), pulmonary rehabilitation (PR) and nutrition counselling. COPD management entails a multidisciplinary team approach and combination of both optimal pharmacologic management and a non-pharmacologic approach. Current guidelines include very few recommendations on the optimal non pharmacologic management for patients with severe COPD, but there are several studies on the non -pharmacologic management of COPD. [6]

In this article, we have discussed the main non-pharmacologic management options for COPD, the evidence based indications for the different options.

2. Smoking Cessation

Smoking is the largest risk factor for the development of COPD in susceptible patients. Both 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 decrease in symptoms, reduction in prevalent symptoms and improvement in health status. [7], [8] Smoking cessation is also the only therapy that has been clearly demonstrated to improve both the rate of lung loss and survival among patients with mild to moderate COPD. [9] Patients at all levels of disease severity should be offered counseling regarding smoking cessation. Unlike the pharmacologic therapies for COPD, the cost-effectiveness of smoking cessation on a population basis is very cost-effective and cost-saving over time. [10], [11], [12], [13] Increased 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 pharmacotherapy and found greater smoking cessation success with this combined approach. [14] Smoking cessation can be approached in several ways ranging from counselling to pharmacologic interventions or both. The U. S. Preventive Services Task Force recommends that clinicians ask all adults patients about tobacco use and that they provide behavioral and pharmacologic interventions to support cessation. [15]

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

The superior strategy for smoking cessation includes counseling with nicotine replacement therapy (NRT) or other pharmacologic therapy. Nicotine replacement therapy tends to be more effective than placebo and can increase long-term rates of abstinence. There are multiple nicotine replacement agents, generally equal in effectiveness. NRTs 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 benefit regarding enhanced potential of cessation. A 2013 systematic review of pharmacological interventions for smoking cessation assessed these therapies, defining long-term abstinence as a period of at least 6 months. [16] NRT and bupropion were found to be superior to placebo. Varenicline was also superior to placebo, as well as to NRT alone and to bupropion alone. 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 and gum) appears to be more effective than using a single agent. [2] Varenicline, compared to other single agents, is reportedly more effective at producing long-term abstinence, [17] however, it is associated with potential significant behavioral side effects. This medication carries an FDA black box warning due to a heightened risk of neuropsychiatric symptoms that may include dream disorder, agitation, depressed mood, or suicidal ideation.

3. Pulmonary Rehabilitation

There has been a strong push towards the use of Pulmonary Rehabilitation (PR) due to the fact that physical activity is a strong predictor of all-cause mortality in COPD. [18] PR focuses on exercise endurance and strengthening to improve dyspnea and health related-quality of life (HR-QOL) in COPD patients. 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. [19] 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, dyspnea, walk distance, and exercise tolerance. [20] 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. [21] 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 is a complex interdisciplinary non-pharmacologic program that varies in composition of staff (table 1) as well as what is offered (table 2). Pulmonary

Rehabilitation must include an initial comprehensive patient assessment in order to determine a best focus for the individualized treatment plan going forward. This assessment usually includes an assessment of disease severity, physiological limitations, functional limitations, and comorbidities in order to set patient-specific goals. [22]

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 pharmacologic and non-pharmacologic treatment)
• Behavioral Change
• Self-Directed Care Planning

In contrast to the length of PR, there has been consensus on the intensity of the exercise during PR. High intensity endurance training is showing benefits over moderate intensity training with regards skeletal muscle strength, respiratory muscle strength, endurance, and dyspnea. [23] The intensity of training tolerated by each patient depends on their baseline COPD severity. No matter what level of intensity can be tolerated, exercise training will still benefit patients with COPD. Specifically emphasizing respiratory muscles training provide insignificant improvements in functional capacity or exercise capacity. Sessions that focus on upper and lower body strength and endurance training are much more preferred. [24] 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 C.M et al. showed that 34% of AECOPD patients discharged from the hospital following an exacerbation are readmitted within 3 months. [25]

More strikingly, up to 25% of patients after an acute exacerbation of COPD may not recover to baseline peak flow. [26] The location of PR after AECOPD may include the inpatient hospital units, (at the time of AECOPD), hospital outpatient units, the community, and at home. All these locations have shown degrees of success, the inpatient and hospital outpatient units are showing the best results but at unsurprisingly high costs.

In COPD, exercise intolerance is a defining limitation and skeletal muscle dysfunction is a defining extra pulmonary manifestation. [27] 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 to the degree of air-flow disease. [28] 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. [29] 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. [30] 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. [31]

3.1. Rollators

Another non-pharmacologic intervention or adjunct in the treatment of COPD is the rollator device (also called the

rolling walker). Rollators are used to assist COPD patients while ambulating by providing a mechanical platform to enhance both motion and rest. A study by Sherra Solway et al. discovered several mechanisms by which the rollator may assist walking including: improving balance, effecting a biomechanical position, stabilizing the chest to allow for improved breathing effort, moving some of the patient's weight to the rollator, and improving pace and walking efficiency. [32] The same study showed that COPD patients with unassisted 6-minute walk distances of less than 300 meters, using rollators increased walking distances and decreased dyspnea during a walk test. As with many interventions, getting patients to engage and maintain these interventions often ends up being one of the major barriers to successful usage.

3.2. 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. [33] 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.

4. 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], [34], [35] 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. [33], [37] Other than the mortality benefits of LTOT, it also improves quality of life, cardiovascular morbidity, depression, cognitive function, exercise capacity, and frequency of hospitalization. [37], [38], [39], [40], [41], [42], [43]

Indications for continuous long-term oxygen therapy for patients with chronic lung disease include:

- 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 such as:

- 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 even in patients who do not significantly desaturate during exercise. [44] Patients with severe disabling shortness of breath may find symptomatic relief with supplemental oxygen. [45]

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

Oxygen supplementation during exercise induces dose-dependent improvements in endurance and symptom perception in non-hypoxaemic COPD patients. [46]

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. [47] Supplemental oxygen may improve shortness of breath and so allowing for greater intensities of exercise training in symptoms limited patients. [48] 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. [49] 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. [50]

The exact role of oxygen as a rehabilitative adjunct remains to be delineated. [34] 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. [51] The proportion of patients who show improvements in exercise performance during a test of hyperoxic exercise need to be appropriately evaluated by clinical trials.

Sleep-related breathing disorders (SRBD) are common in patients with COPD occurring in approximately 40 percent of patients. [52] Patients who have nocturnal oxygen desaturation should be evaluated for sleep-disordered breathing. The management of nocturnal desaturation should be determined by the cause.

The prescription of LTOT has rare adverse effect for

patients with COPD if administered correctly. [53] Facial and upper airway burns are an infrequent complication of LTOT, but can be severe and potentially life-threatening. [54], [55], [56], [57] Patients should not smoke while using supplemental oxygen. [57] Oxygen should be kept at least six feet (two meters) away from any open flame, or sources of sparks. 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. [58]

5. NPPV

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 severe dyspnea with clinical signs of respiratory muscle fatigue, increased work of breathing, and respiratory acidosis (arterial pH ≤7.35 and arterial tension of carbon dioxide [PaCO2] ≥45 mmHg [≥6 kPa]).[2]

Several studies have shown that NPPV improves important clinical outcomes in patients having an acute exacerbation of COPD complicated by hypercapnic acidosis. [59], [60], [61], [62], [63] 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 (PaCO2 >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. These studies also demonstrate that patients with severe exacerbations of COPD respond better to NPPV than patients with mild COPD exacerbations. [60], [61], [62], [63], [64], [65] NPPV is superior to medical therapy alone for the management of severe exacerbations of COPD. [66], [67], [68], [69], [70] One year mortality was reported to be lower in patients receiving NPPV for exacerbations of COPD than patients receiving either optimal medical therapy alone [68] or conventional mechanical ventilation. [69] COPD patients who develop respiratory failure should be placed on NPPV given its proven decrease in morbidity, mortality and 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. [71] Patients with advanced COPD who are not candidates for active resuscitation or ICU admission may still benefit from NPPV in the general ward with up to 60% hospital survival. [72] 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. [71] 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 an increased minute ventilation. [73] 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 compared to patients who were on the standard treatment. Patients on NPPV however did show improvements in daytime PaCO2 and nocturnal transcutaneous PaCO2 measurements. [74]

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. [75] NPPV has been used during exercise training in COPD patients [76], [77] and especially during pulmonary rehabilitation. NPPV increases minute ventilation despite reduced inspiratory effort during pulmonary rehabilitation. [78] With an increase in minute ventilation, NPPV unloads inspiratory muscles, [79], [80] and prolongs exercise induced lactatemia, [81] leading to reduced shortness of breath on exertion and improving exercise tolerance. [78], [82], [83], [84], [85], [86], [87], [88]Adding NPPV to exercise training in patients with stable hypercapnic COPD improves PaCO2, 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. [45], [89], [90], [91] Nava et al. performed a survey on patients in an intermediate respiratory care unit. This survey revealed that one third of patients with poor life expectancy use NPPV. [92] 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. [93]

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

6. Surgical Interventions

The main surgical options used for the treatment of COPD are bullectomy, lung volume reduction surgery (LVRS), and lung transplantation. Unfortunately, most patients with COPD are not surgical candidates. In order for a COPD patient to undergo any surgical procedure, they have to be carefully selected and must meet the criteria for surgical intervention for the benefits of the surgery to outweigh the harm. These procedures are reserved only to patients who remain symptomatic despite optimal medical treatment. In fact most patients considered for surgery are symptomatic with shortness of breath, pain, or spontaneous pneumothorax. [94]

6.1. Bullectomy

This is the removal of a large bulla that does not contributing to gas exchange, thus decompressing the adjacent lung parenchyma. A bulla is defined as an air space in the lung measuring more than one centimeter in diameter in the distended state. A giant bulla is one that occupies at least 30 percent of a hemithorax. [95], [96], [97] Prior to performing bullectomy on any patient, it is very important to estimate the effect of the bulla on the lung and the function of the remaining lung. In carefully selected patients, bullectomy can reduce shortness of breath and improve lung function. [98] Patients with a single bulla occupying at least half the volume of the pleural cavity would be considered candidates for surgery, while patients with smaller lesions and no symptoms would be more controversial. [94]

Bullectomy can be performed as a thoracoscopic procedure, but the technique of the operation is quite variable and depends on the anatomical details of the bulla as well as the preferred approach of the surgeon. Formal lobectomy seems to be a less attractive option to most surgeons. [94] Parenchymal air leaks are the biggest single postoperative complication and can generally be appropriately managed with options like buttressed stapled lines, pleural tent, pleurectomy, biological glues, or ambulatory Heimlich valves. All patients with emphysema seem to experience a progressive decline in FEV_1 over time, so patients with near normal underlying lung at the time of bullectomy will begin at a higher functional baseline than those with moderate or severe emphysema in the remaining lung. [94]

6.2. Lung Volume Reduction Surgery

Lung volume reduction surgery (LVRS) also known as reduction pneumoplasty, is a surgical intervention that consist of reducing the lung volume by wedge excision of emphysematous tissue. It is a surgical intervention that could be beneficial and preferred in some patients with poorly controlled advanced emphysema despite optimal medical therapy Lung volume reduction surgery (LVRS) is a treatment option in selected COPD patients with emphysema. LVRS could be bilateral or unilateral. LVRS improves breathing mechanics and lung function. [99] Diaphragm length and trans-diaphragmatic pressures improve after LVRS, resulting in improvements in exercise capacity, dyspnea, and quality of life. [100], [101] Lung recoil and ventilatory drive also improve after LVRS. [102], [103], [104]

Both health and general quality of life also improved in patients who underwent LVRS. Their quality of sleep and neurobehavioral functioning also improved. [105], [106], [107], [108]

Fishman et al conducted a randomized trial on 1218 patients comparing lung-volume-reduction surgery with medical therapy for severe emphysema. They noted that lung-volume-reduction surgery increases the chance of improved exercise capacity but does not confer a survival advantage over medical therapy. Secondly, LVRS yields a survival advantage for patients with both predominantly upper-lobe emphysema and low base-line exercise capacity. Patients for LVRS must be appropriately selected in order to reap any benefits from the surgery. Patients who were previously reported to be at high risk or have a high base-line exercise capacity or non-upper-lobe emphysema were found to have increased mortality and negligible functional gain. [109]

LVRS reduces the size of mismatching between the hyper-inflated lungs and the chest cavity, thus increasing elastic recoil, improving expiratory airflow. [110], [111], [112], [113], [114], [115] and returning the diaphragm to a more normal curved and lengthened configuration. [116], [117] Secondly with the reduction of lung volumes there is also a reduction in dynamic hyperinflation during physical exercise leading to an improvement in exertional dyspnea. [113] VRS decreases intrathoracic pressures, thus improving left ventricular filling, end-diastolic dimension, and cardiac index. [118] Clarenbach et al. conducted a randomized controlled trial in 30 patients with severe COPD and emphysema scheduled for LVRS and found that endothelial function and blood pressure improved 3 months after LVRS in these patients. [119] Exercise capacity also improves after LVRS. The six-minute-walk distance increases from an average of 1,239 to 1,286 feet a month. After LVRS, FEV1 increases from about 28.1% predicted to 36.2%. The improvement is greatest at 6 months. [105]

Prior to performing LVRS, pulmonary function tests, a six-minute walk test, an arterial blood gas, electrocardiogram, an echocardiogram with measurement of pulmonary artery pressures, a cardiopulmonary exercise test, and a high resolution computed tomography (HRCT) have to be completed. These tests will aid in determining the most appropriate patients for LVRS based on the indications noted on table 3 and may also aid in the differential diagnosis of shortness of breath.

Other than the indications to LVRS noted on table 3, LVRS can also per performed as a bridge to transplantation. Unilateral LVRS can be performed early post-transplant to

treat acute native lung hyper expansion or late to treat chronic native lung hyperexpansion. In addition, unilateral LVRS can be performed simultaneously with single lung transplantation to prevent native lung hyper expansion.

Table 3. *Indications for Unilateral LVRS and bilateral LVRS.*

Indications for unilateral LVRS. [119]	Indications for bilateral LVRS. [110], [120], [121], [122]
• unilateral asymmetric emphysema, • severely asymmetric emphysema • contralateral pleurodesis, contralateral thoracotomy, hemodynamic instability massive air leak during the first side of a planned bilateral LVRS • severe native lung hyperinflation after single lung transplantation for emphysema	• Age <75 years • Ex-smoker (4-6 months) • Clinical picture consistent with emphysema • Disability despite maximal medical therapy and pulmonary rehabilitation • Absence of clinically significant bronchiectasis and absence of high daily production of sputum • FEV1 after bronchodilator <45 percent predicted • Hyperinflation (TLC >100 percent predicted, RV >150 percent) • Post rehabilitation 6-minute walk distance >140 meters • Low post rehabilitation maximal achieved cycle • Chest radiograph - hyperinflation • HRCT confirming severe emphysema • Upper lobe predominant emphysema • Six minute walk distance >140m

FEV1: forced expiratory volume in one second, TLC: total lung capacity; RV: residual volume, PaO2: arterial partial pressure of oxygen; PaCO2: arterial partial pressure of carbon dioxide; HRCT: high resolution computed tomography.

Table 4. *Contraindications to LVRS.*

Contraindications to LVRS. [120], [122], [123]
• Age ≥75 years
• Current smoking
• Comorbid disease with risk of life expectancy <2years
• Severe obesity (BMI>31.1 in men and 32.2 in women) or cachexia.
• Surgical constraints (eg, previous thoracic procedure, pleurodesis, chest wall deformity)
• Pulmonary hypertension (PA systolic >45 mmHg, PA mean >35 mmHg)
• Clinically significant bronchiectasis
• Clinically significant coronary heart disease
• Heart failure with an ejection fraction <45 percent
• Giant bulla taking up more than 30% of the lung in which it is located
• Oxygen requirement of >60 per min to maintain saturations of 90% or above
• Extensive pleural symphysis from pleural disease or previous chest surgery
• Daily use of prednisone
• Uncontrolled hypertension
• FEV1 ≤20 percent predicted with either DLCO ≤20 percent predicted or homogeneous emphysema
• PaO2 ≤45 mmHg on room air
• PaCO2 ≥60 mmHg
• Homogeneous emphysema with FEV1 ≤20 percent predicted
• Significant pleural or interstitial changes on HRCT
• Non-upper lobe predominant emphysema
• High post rehabilitation maximal achieved cycle

FEV1: forced expiratory volume in one second, TLC: total lung capacity; RV: residual volume, PaO2: arterial partial pressure of oxygen; PaCO2: arterial partial pressure of carbon dioxide; HRCT: high resolution computed tomography.

Major short-term complications of lung volume reduction surgery (LVRS) include death, reintubation, arrhythmias, mechanical ventilation for more than two days, pneumonia, and persistent air leak. LVRS is substantially more expensive than medical therapy. In an updated analysis to the Nett study, Ramsey SD et al. reported the cost-effectiveness of LVRS versus medical therapy of USD $140,000 per quality-adjusted life-year (QALY) gained (95% CI, $40,155 to $239,359) at 5 years, and was projected to be $54,000 per QALY gained at 10 years. In subgroup analysis, the cost-effectiveness of LVRS in patients with upper-lobe emphysema and low exercise capacity was $77,000 per QALY gained at 5 years, and was projected to be $48,000 per QALY at 10 years.[124] Postoperative in-hospital stay after LVRS is about 10 days. Survival after LVRS is approximating 90% at 1 year, 77% at 3 years, and 65% at 5 years. Patients with upper lobe predominant disease have a relatively better outcome. [105]

Table 5. *Ninety-day mortality after LVRS.*

Ninety-day mortality after LVRS percentage of patients. [105]
• Respiratory cause in 43%
• Cardiovascular cause in 18%
• Multisystem organ failure in 7%
• Cerebrovascular abnormalities in 4%
• Unclassified in 25%

6.3. Lung Transplantation

Lung transplantation was initially used as treatment for pulmonary fibrosis and pulmonary hypertension, but the

indications have evolved such that emphysema is the most common diagnosis leading to transplantation today. Lung transplantation for COPD and α_1-antitrypsin deficiency accounted for 60% of the almost 17,000 lung transplantations performed worldwide over the last decade. [125] The effect of lung transplantation on the survival of patients with COPD is not yet settled. Results from "The twenty-fourth official adult lung and heart-lung transplantation report-2007 from the Registry of the International Society for Heart and Lung Transplantation" found a post-transplantation survival for patients with COPD of 81.5% at 1 year, 64.0% at 3 years, and 49.0% at 5 years. [125] In fact for younger patients receiving bilateral lung transplantation, the survival is 94.9, 84.7, and 68.2% in those less than 50 years of age, and 93.0, 79.7, and 60.5% for those between ages 50 and 60 years at 1, 2, and 3 years, respectively. [126] In May 2005 a lung allocation system was created in the United States, with aims to prioritize patients who are most likely to die on the waiting list. The goal is to optimize overall survival benefit rather than to continue the prior, less discriminating, listing system based on waiting time. [127] Efforts like this and other efforts have been implemented to help select patients who will benefit the most from transplant. Lung transplant improves survival in appropriately selected patients. Lung transplantation also improves exercise tolerance and quality of life in patients with severe COPD. [128]

Appropriate patients for lung transplant include patients whose predicted disease-related survival based on the Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity (BODE) index is worse than the predicted survival after transplantation. [129] Patients with a BODE index score of 7–10 have a median survival of about 3 years and should be evaluated for transplantation. Secondly, patients who are hospitalized with COPD exacerbation complicated by hypercapnia (PaCO2 >50 mm Hg), who have a 2-year survival of only 49% should also be evaluated for lung transplantation. [130] Thirdly, patients with emphysema with FEV1 < 20% predicted and either homogeneous disease on high-resolution computed tomography scan (HRCT) or diffusion capacity (DLCO) < 20% predicted have a median survival of about 3 years with medical therapy and are at high risk of death after LVRS with little chance of functional benefit patients should be considered for transplantation. [105] Also patients who have multiple co morbidities or patients with pulmonary hypertension, hypoxemia, hypercapnia, and multiple disease exacerbations have reduced survival rates, [131], [132] and so should be considered for lung transplantation. Lung transplantation consists of a morbid surgical procedure followed by life-long immunosuppressive therapy. Candidates for lung transplantation should have the support system to be able to go through the process. (Table 6)

Table 6. *Selection of candidates for lung transplantation.*

Who should be evaluated for lung transplantation?
• Patients with severe COPD who remain symptomatic despite optimal medical therapy
• Candidates whose predicted disease-related survival is less than the predicted survival after transplantation (81.5, 64.0, and 49.0% at 1, 3, and 5 yr, respectively). [125]
• Patients who are hospitalized with a COPD exacerbation complicated by hypercapnia (PaCO2 ≥ 50 mm Hg), who have a 2-year survival of only 49%. [129]
• Patients with a BODE index score of 7–10 (have a median survival of about 3 years)
• Patients with a median survival of about 3 years with medical therapy, high risk of death after LVRS with little chance of functional benefit.[105]
• Patients with additional risk factors for reduced survival (pulmonary hypertension, hypoxemia, and hypercapnia, and multiple disease exacerbations). [132]
• Patients with α1-antitrypsin deficiency

Table 7. *When to consider lung transplantation over LVRS.*

When to consider lung transplantation over LVRS.[128]
• FEV1 ≤20% predicted and either homogeneous disease or DLCO ≤20% predicted
• Lack of emphysema on HRCT
• TLC < 100% predicted
• RV < 150% predicted
• PaCO2 > 55 - 60 mm Hg
• PaO2 < 45 mm Hg
• 6MWD≤140 m, < 3 min unloaded pedaling on cycle ergometer
• Pulmonary hypertension
• Clinically significant bronchiectasis and/or recurrent pulmonary infections

6MWD: distance walked in 6 minutes; Dl_{CO}: diffusion capacity of carbon monoxide; HRCT: high-resolution computed tomography; LVRS: lung volume reduction surgery; RV: residual volume; TLC: total lung capacity.

Pulmonary function and gas exchange drastically improve after lung transplant. Hypoxemia and hypercapnia improve significantly and return to normal or near-normal values and almost all patients remain free of supplemental oxygen. [133], [134], [135] FEV1 increases from 15–20% predicted to 80–90% predicted in bilateral lung transplantation and to 50–60% predicted in ingle lung transplantation. [133], [134], [135], [136] Exercise capacity increases after transplantation. The six-minute-walk distance doubles by 3–6 months after surgery, going from about 700–900 feet to about 1,300–1,700 feet. [134], [135], [137]

Trans diaphragmatic pressures improve with maximal sniff

after lung transplantation, compared with similar patients with COPD not undergoing transplantation. [138]

There are sustained improvements in multiple dimensions of quality of life after lung transplantation including physical functioning, role function, social function, mental health, and health perceptions. Up to 90% of patients were satisfied by their decision to undergo transplantation. [139]

Lung transplantation results in greater short-term mortality and morbidity, a longer postoperative course and a predicted lower long-term survival as compared with patients undergoing LVRS, with a hazard ratio of 1.7. [140] This could be partly due to the fact that patients who undergo lung transplantation usually have more severe airflow obstruction with a mean FEV1 of 23.6 ± 8.5 vs. 31.9 ± 17%. Diaphragm dysfunction occurs in about 3.2–42.8% of patients after transplantation, possibly because of phrenic nerve dysfunction. [141]

Late post-transplantation complications such as bronchiolitis obliterans syndrome are frequent in patients who undergo lung transplant. The procedure is generally of longer duration, with a more frequent requirement for cardiopulmonary bypass. [137], [142], [143], [144] Lung transplantation patients tend to have a longer hospital stay and more outpatient visits compared with patients undergoing LVRS. [140] Postoperative in-hospital stay after lung transplantation is 16–35 days as compared to just 10 days for LVRS.

Causes of early mortality after transplantation (within 30 days). [125]

- Graft failure (28.3%)
- Non cytomegalovirus infections (20.3%)
- Cardiovascular complications (10.8%)
- Technical issues (8.2%)
- Acute rejection (4.7%

Table 8. *Absolute and Relative contraindications to lung transplantations.*

Absolute contraindications	Relative contraindications:
• Comorbidities that precluding appropriate immunosuppressive therapy such as renal insufficiency, liver dysfunction, neuropathy, significant • osteoporosis and uncontrolled diabetes • Chronic active viral hepatitis B, hepatitis C with biopsy-proven histologic evidence of liver disease • HIV infection • Lack of social support • Psychiatric conditions limiting long-term compliance • Inability to maintain long-term follow-up • Malignancy (with the exception of cutaneous squamous and basal cell tumors) • Refractory gastroesophageal reflux disease • Significant chest wall or spinal deformity • Active substance use disorder or within the last 6 months	• Age older than 65 years • Critical or unstable clinical condition (e.g., shock, • mechanical ventilation or ECMO) • Severely limited functional status with poor • rehabilitation potential • Colonization with highly resistant or highly virulent bacteria, fungi or mycobacteria • Severe obesity defined as a BMI exceeding 30 kg/m^2 • Chronic mechanical ventilation • Unstable extrapulmonary medical conditions that have not resulted in end-stage organ damage

7. Nutrition

Weight loss is an independent predictor of morbidity, [145], [146] and mortality in patients with COPD, [147], [148], [149], [150] and evidence suggest that weight gain can reverse this increased mortality risk. [149]

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. Depletion of FFM is a significant problem in hospitalized patients with severe COPD, [151] as well as in outpatients with moderate airflow obstruction. [152] The causes of weight loss in COPD are multifactorial ranging from eating difficulties, [150], [153] higher metabolic rate and cost of ventilation, [154] to oxidative stress causing systemic inflammation. [155], [156]

Weight loss as a result of imbalance between increased energy demand and/or reduced dietary intake is a common and serious problem for patients with COPD. [157] 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. [158] 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.

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. [159] 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 are of major importance in these patients, but nutrition therapy may only be effective if combined with exercise or other anabolic stimuli. [159], [160]

Pulmonary Rehabilitation programs include nutrition counseling to encourage more appropriate dietary regimens and weight maintenance. Studies suggest that there may be some benefits 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 to this approach. [161]

8. 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. [162]

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. [163]

9. Integrative Medicine: Tai Chi and Acupuncture

Integrative Medicine has emerged to complement many fields of medicine and COPD is also represented. Tai Chi for COPD was reviewed recently, [164] and revealed that Tai Chi participants were able to walk further and had better pulmonary function than those receiving usual care; however, there was no apparent improvement in QOL. Additionally, when comparing Tai Chi with exercise to exercise alone, there was no additional benefit noted. Tai Chi may be added safely to a comprehensive PR program, but additional studies are needed to determine if there will be any additional tangible benefits over standard exercise. For those patients unable to tolerate usual PR exercise, Tai Chi may be an alternative given its similar effectiveness. [165] Respiratory disorders such as COPD often produce anxiety and studies of acupuncture in the setting of anxiety, albeit limited, have been reviewed, and have shown promising findings as an adjunctive treatment for anxiety. [166] This raises the possibility for a future role for acupuncture in COPD with anxiety but further research is necessary before it can be recommended as part of evidence based care.

9.1. 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 try to ensure patients are educated in self-management skills, decision-making during COPD exacerbations, and facilitate discussions regarding advanced directives and end-of-life issues. These are among 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. [167] Additionally, when appropriate, patients may benefit from referral to mental health providers for more specific therapeutic interventions aimed at helping them cope with their 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. [168] 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 the quality of their life.

9.2. Palliative Care

Patients with COPD that are appropriate for palliative care will note that both pulmonary rehabilitation and palliative care have similarities (Table 9). Both require multidisciplinary teams that focus on specific individual needs regarding relief of symptoms, improvements in functional status, and improvements in quality of life. The focus should be to aim for the right treatment for the right patient at the right time. The similarities of palliative care and pulmonary rehabilitation go beyond their primary focuses: palliative care, similarly to pulmonary rehabilitation, has been shown to actually improve some COPD patient metrics and thus there is an overlap in the two treatment modalities.

Table 9. *Pulmonary rehabilitation vs Palliative care.*

	Pulmonary Rehabilitation	**Palliative Care**
Stage of Disease Targeted	All stages	All stages
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, thus predicting survival in the disease is of great importance. [169] Dajczman et al. showed that the 6MWT can be used to predict 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. [170]

Given the challenges of determining an accurate prognosis in COPD patients, PC should be offered to all chronic severe COPD patients who remain symptomatic and have functional

limitations. PC is beneficial to any stage of COPD (acute, chronic, or terminal). [171] Other recommended triggers to use to prompt PC initiation or intensification are listed on table 10.

Table 10. *Triggers prompting the Palliative care.*

Triggers Prompting Palliative Care Initiation or Intensification. [171]
Multiple Hospitalizations
Decline in Functional Status (ADLs)
Disabling Dyspnea
FEV1 < 30%
Oxygen Saturation < 88%
PaCO2 > 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 palliative care consultation or intensification. This question has been shown to identify patients with poor prognoses in cancer patients, [172] and it may be helpful in other diagnoses. Studies are needed on question for patients with COPD in order for us to have definitive answers.

The primary symptoms of COPD patients targeted by palliative care are fatigue, cough, dry mouth, pain, refractory breathlessness, anxiety, depression, and decreased quality of life. Palliative care for the COPD patient is complicated by cough, dry mouth, and breathlessness which can cause communication difficulties. The healthcare team must be vigilant in recognizing the need to act towards symptom relief. It has been shown, that COPD patients receive less palliative care and more aggressive care compared to those, say, with lung cancer. [173] Some of the specific treatments recommended for COPD patients requiring palliative care are pharmacologic therapy (including opioids), physical rehabilitation, oxygen therapy, and noninvasive ventilation for symptoms like dyspnea. Physical rehabilitation and pharmacologic therapy (including sedation) may be required for the treatment of anxiety and depression. [174]

Due to the challenges in predicting mortality in COPD along with the communication challenges in COPD patients, palliative care 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.

10. 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 the pharmacologic management. Current pharmacologic managements are unable to cure COPD. Non pharmacologic management provides significant benefits to patients with severe COPD who are symptomatic despite being on optimal medical therapy. The main goals of non-pharmacologic 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 pharmacology 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-pharmacologic management of COPD.

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