Chronic Obstructive Pulmonary Disease: A Review of Nonpharmacologic Therapies
Maria Srinivasan, MD, and Shirin Shafazand, MD, MS

ABSTRACT

• **Objective:** To provide an evidence-based review of the important nonpharmacologic therapies in the care of patients with chronic obstructive pulmonary disease (COPD).
• **Methods:** Literature review.
• **Results:** COPD, including emphysema and chronic bronchitis, is the fourth leading cause of death in the United States. COPD represents a significant economic burden both for individuals and for society. COPD is a chronic, systemic disease requiring a multidisciplinary and multimodal approach to its care and management. Treatment approaches include a combination of pharmacologic and nonpharmacologic therapies applied in a step-wise fashion based on airflow limitation severity criteria and patient symptoms. Smoking cessation, vaccinations, maintaining physical activity, adequate nutrition, reducing occupational and environmental exposures, and ensuring psychological health are the cornerstones of long-term management of COPD.
• **Conclusion:** The care of patients with COPD requires a multidisciplinary approach that involves not only pharmacologic therapies but also meticulous attention to the physical, social, and psychological well being of the individual. An individualized prescription of nonpharmacologic therapies is necessary to address the systemic disease that is COPD.

Chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis, is the fourth leading cause of death in the United States and the mortality rate is anticipated to increase in the next decade, especially among women [1]. COPD represents a significant economic burden both for individuals and for society. According to estimates made by the National Heart Lung and Blood Institute (NHLBI) in 2007, the annual cost in the United States for COPD/asthma/pneumonia was $85 billion, which included $66 billion in direct health care expenditures and $19 billion in indirect mortality costs [2].

The third National Health and Nutritional Survey (NHANES) reported that among people 25 to 75 years of age, the prevalence of mild COPD was 6.9% and the prevalence of moderate COPD was 6.6%. The 2011 National Center for Health Statistics (NCHS) data estimates COPD prevalence among people older than 18 years to be 5.1%, a rate that has been stable from 1998 to 2009. The prevalence of the disease increases with age and is higher among women compared with men across all age-groups up to age 75 [3]. However, while the hospitalization rate has decreased over the past decade for both sexes, the death rate has declined only for men [3].

COPD is a systemic and chronic disease [1], requiring a multidisciplinary and multimodal approach to its care and management. Treatment approaches include a combination of pharmacologic and nonpharmacologic therapies applied in a step-wise fashion based on airflow limitation severity criteria and patient symptoms. Smoking cessation, vaccinations, maintaining physical activity, adequate nutrition, reducing occupational and environmental exposures, and ensuring psychological health are the cornerstones of long-term management of COPD.

In this article we provide an evidence-based review of the important nonpharmacologic therapies in the care of patients with COPD.

NONPHARMACOLOGIC THERAPIES

**Smoking Cessation**

Smoking is the only known preventable risk factor, with consequent increases in both morbidity and mortality attributed to continuation of smoking [4].

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The US Department of Health and Human Services [5,6] and World Health Organization identify cigarette smoking as an “addictive” and relapsing disorder. Treating it prior to disease onset is considered primary prevention. More often than not, clinicians are faced with treating this addiction after the onset of COPD, and with the occurrence of other smoking-related disorders including cardiovascular disease (CVD).

It is important to note that although cigarette smoking is an important risk factor for COPD, a recent report from the BOLD study (Burden of Obstructive Lung Disease) showed that 23.3% of patients classified as having mild to moderate COPD were nonsmokers [7]; this is in keeping with estimates from NHANES III, where approximately one-fourth of patients with COPD had no prior smoking history [8]. The best predictors for developing COPD in these nonsmokers were lower education level, increased age, prior diagnosis of asthma, more than 10 years of occupational exposure to organic dusts in women, and body mass index (BMI) less than 20 kg/m² [7]. Nonsmokers have less severe COPD than current or ex-smokers.

COPD can be viewed as an imbalance between factors that cause destruction of the airways and lung parenchyma and available reparative processes (supported by alpha1-antitrypsin, neutrophils, macrophages) [9]. Studies support cigarette smoke as the initiating factor in the cascade that leads to disease development, causing release of inflammatory mediators from the epithelial cells, with consequent destruction of epithelial and endothelial cells and of extracellular matrix, followed by activation of alveolar macrophages, neutrophils and immature dendritic cells (as part of the innate immune response), with continuous damage to the lung tissue [10–12].

Smoking-related morbidity and mortality are attributed mostly to the development of CVD, lung cancer, and COPD. Several studies have evaluated the impact of smoking and smoking cessation on these conditions, including the Lung Health Study (LHS) [13,14], the Multiple Risk Factor Trial (MRFIT) [15], INTERHEART study [16], and Survival and Ventricular Enlargement (SAVE) study [17]. In the LHS, smoking cessation was associated with a slower decline in lung function, evidenced by a decrease in forced expiratory volume in the first second of expiration (FEV₁) from 63 mL/year in continuous smokers to 34 mL/year in sustained quitters over a period of 5 years, compared with the age-related natural decline of FEV₁ of 30 mL/year in persons who never smoked [13]. Although the rate of decline in lung function is greater in females compared with males for the same pack-year of smoking, in this study, smoking cessation had the greatest impact on slowing the decline in lung function in females compared with males. LHS showed no significant difference in total mortality rate or rate of hospitalizations for respiratory disease among patients (regardless of smoking cessation intervention) [14], while MRFIT showed a 19% reduction in death from respiratory causes in the intervention arm (consisting of reductions in cholesterol, diastolic blood pressure, and smoking cessation counseling) [15].

Lung cancer is related to cigarette smoking in 90% of cases [18]. A meta-analysis of 10 observational studies showed that smoking cessation at the time of diagnosis of early lung cancer decreased recurrence rates, development of secondary primary cancers, and all-cause mortality when compared with patients who continued to smoke after diagnosis [19].

The benefits of smoking cessation are clearly understood; however, the addictive nature of this disorder has made its treatment a challenge. Among the predictors of success for prolonged abstinence are enrollment in smoking cessation programs [13], older age, and lower pack-year smoking history [4]. Interventions for addiction treatment are classified as non-pharmacological (intensive counseling) and pharmacologic, with synergistic activity when both methods are used. The diagnosis of COPD with spirometry values presented as “lung age” (defined as the age of an average person with FEV₁ similar to patient’s FEV₁) is a good opportunity to encourage patients to quit smoking [4].

All health care providers should enquire about smoking habits, assess readiness to quit, and provide brief counseling at each visit. The severity of smoking dependence can be evaluated with the Fagerstrom Test for Nicotine Dependence, which can be used by the primary care physician as part of the smoking cessation intervention [20]. The 5 “As” approach may prove useful: (1) ASK: Enquire about smoking habits at each visit, (2) ADVISE: Strongly advise all smokers to quit, (3) ASSESS: Determine willingness to quit, (4) ASSIST: Help the patient to quit by referring for further counseling, and provide pharmacotherapy, and (5) ARRANGE: Provide follow-up.

The most commonly used pharmacologic therapies for smoking cessation include nicotine replacement therapy (NRT; gums, patches, inhalers, lozenges, sublingual tablets, and nasal sprays), antidepressants (bupropion), and
varenicline. Mechanism of action, dosage, and commonly reported side effects of these pharmacologic options are provided in Table 1. All forms of NRT and bupropion have similar efficacy, increasing the rate of persistent abstinence at 6 months by two-fold [21–23]. It is unclear whether bupropion is superior to NRT, or whether combination therapy is more successful than either alone. The use of varenicline for 12 weeks was associated with an increase in abstinence rate from 9% in the placebo group to 42% in the treatment group, which decreased to 19% in the treatment group and 6% in the placebo group at 52 weeks [24]. NRT was not used in this study. Although the literature is limited, there is some suggestion that varenicline is more effective than bupropion in maintaining abstinence at 3 and 12 months [25,26]. However, more studies are needed before one medication can be recommended over the other. Therapy should be individualized with side effects of medications monitored closely.

Vaccinations
The most common pathogens involved in acute COPD exacerbations are influenza virus and *Streptococcus pneumoniae* [27]. By virtue of their role in exacerbations and progression of chronic inflammation, these organisms have a significant impact on COPD morbidity and mortality and have been the focus of vaccination efforts. Older observational studies and recent Cochrane reviews of randomized trials for influenza and pneumococcal vaccines have shown a reduction in acute COPD exacerbations with influenza vaccination [28] but not with pneumococcal vaccination. There is no strong evidence for reduction in hospitalization or mortality rates with the use of either vaccine [28,29]. Supported by observational studies only and not confirmed by randomized controlled trials [30], current guideline recommendations are that all patients with COPD should receive both influenza and pneumococcal vaccines. There is some evidence for the additive effect of the 2 vaccines, with one retrospective longitudinal study showing a 63% reduction in the risk of hospitalizations and an 81% reduction in the risk of death when both vaccines were administered in COPD patients [31–33].

Pulmonary Rehabilitation
Skeletal muscle strength in COPD plays an important role in the physical well being and functional ability of the individual. Studies have shown that in some patients, muscle fatigue rather than dyspnea is the limiting factor in exercise capacity [34]. In COPD patients, muscle fatigue develops at activity levels much lower than healthy controls, an idea further supported by the observation that even patients with minimal airway obstruction develop exercise intolerance [35].

**Table 1. Pharmacotherapy for Smoking Cessation**

<table>
<thead>
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<th>Medication</th>
<th>Mechanism of Action</th>
<th>Dose</th>
<th>Side Effects</th>
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| Nicotine replacement therapy | Steady stimulation of nicotinic receptors, with decreased fluctuation in dopamine release in the forebrain | • Inhaler: 6–16 cartridges/day  
  • Gum/lozenge: 2–4 mg oral every 1–2h for 6 weeks, then every 2–4h for 3 weeks, then every 4–8h for 3 weeks  
  • Patch: 14- or 21-mg patch daily for 6 weeks, then taper  
  • Nasal spray: 0.5–1 mg spray each nostril every 1 h, and taper after 8 weeks | Seizures, headache, constipation, changes in taste                   |
| Bupropion                   | Inhibits re-uptake of dopamine and epinephrine in the brain                          | Start with 150 mg orally daily for 3 days, then 300 mg orally daily | Seizures, insomnia, behavioral changes (agitation, hostility, depression) |
| Varenicline                 | Nicotinic receptor agonist, with decreased release of dopamine in the forebrain, preventing stimulation of these receptors by nicotine | Start with 0.5 mg orally daily for 3 days, then 0.5 mg orally twice daily for 4 days, and then 1 mg orally twice daily for total of 12 weeks | Nausea, abdominal cramps, sleep disorders, suicidal ideation |
In 1999, pulmonary rehabilitation was defined by the American Thoracic Society (ATS) as “a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy” [36]. In 2007, an updated definition underlines the multidisciplinary approach and the need for an individualized focus on physical and social function [37]. Pulmonary rehabilitation programs are designed to improve physical exercise capacity, decrease exertional dyspnea, enhance airway clearance, and bring about behavioral changes [38]. Physical exercise capacity can be modulated through endurance or strength training exercises or a combination of these, either as continuous or interval training [39], with or without upper extremity training [40]. To improve exertional dyspnea, the goal of pulmonary rehabilitation is either to decrease the work of breathing (a decrease in exercise-induced hyperinflation) or increase ventilatory capacity, both of which can be achieved through varying modalities (“breathing exercises”) [38]: pursed-lip breathing, slow and deep respiration, active control of expiration, and inspiratory or expiratory muscle training. For airway clearance, forced expiration, chest physiotherapy (manual percussion or mechanical vibrations), positive expiratory pressure breathing, or positive pressure oscillative breathing is often recommended.

In 2006, a Cochrane review of 31 studies was performed to offer a more objective, evidence-based evaluation of the benefits of pulmonary rehabilitation. All included studies were randomized controlled trials (RCTs) involving programs of at least 4 weeks’ duration in an inpatient, outpatient, or home-based setting. The primary outcome measure was the influence of pulmonary rehabilitation on health-related quality of life (HRQOL) and exercise capacity (both maximal exercise capacity expressed as workload or energy consumption and functional exercise capacity expressed as a timed walk test). The systematic review demonstrated a benefit with pulmonary rehabilitation in all domains of HRQOL when compared with standard COPD treatment. There also was an improvement in functional exercise capacity, but the benefit on maximal exercise capacity was not clearly defined. While this systematic review provides objective evidence for the benefit of pulmonary rehabilitation, it does not offer enough information on which components of pulmonary rehabilitation are the most beneficial [41].

While the bulk of the evidence supports the positive role of pulmonary rehabilitation in COPD management, many questions remain unanswered, including the optimal duration of therapy necessary to achieve long lasting results and the particular subtype of muscle training yielding maximum benefit. The American College of Chest Physicians (ACCP) guidelines, while acknowledging the lack of consensus, recommend at least 12 weeks of training [37]. In 2011, a meta-analysis of 5 RCTs including a total of 451 patients enrolled in programs ranging from 4 weeks to 18 months in duration concluded that longer rehabilitation programs are more beneficial in improving HRQOL, but no clear benefit was demonstrated for exercise capacity. Currently, the American College of Sports Medicine guidelines recommend a period of at least 16 weeks of rehabilitation for patients with COPD [42].

Pulmonary rehabilitation has been shown to be beneficial in patients with stable COPD, with recent evidence suggesting a positive impact regardless of severity of disease [43]. An interesting question is whether rehabilitation has any role in the management of patients with an acute COPD exacerbation. A 2010 meta-analysis of 9 RCTs (involving 432 patients) of pulmonary rehabilitation started as inpatient or outpatient within 3 weeks of an acute exacerbation summarizes the evidence to date. The primary outcome was the rate of rehospitalization during the follow-up period (3 to 18 months in different studies), and secondary outcomes included HRQOL, maximal and functional exercise capacity, frequency of outpatient visits, length of readmissions, and mortality. Five of the 9 studies included showed a decrease in the odds ratio (OR) of hospital readmissions (OR, 0.22), with a number needed to treat (NNT) of 4 to prevent 1 readmission over the 25 week median follow-up period. HRQOL and exercise capacity both showed improvement with early implementation of pulmonary rehabilitation after acute exacerbation. These conclusions, while intriguing, would benefit from the addition of more rigorous and larger clinical trials prior to generalized adoption [44].

Long-Term Oxygen Therapy
Long-term oxygen therapy (LTOT) is frequently prescribed for COPD patients. There is evidence for increased survival in patients with severe hypoxemia (defined as $\text{P}_{\text{a}} \leq 55 \text{ mm Hg}$ or $\text{P}_{\text{a}} < 59 \text{ mm Hg}$ with cor pulmonale or polycythemia) with continuous oxygen use [45,46]. This benefit was noted only if $\text{P}_{\text{a}}$ increased $> 65 \text{ mm Hg}$ with therapy, with worse
response in patients with reduced lung carbon monoxide diffusion capacity (DLCO), higher degree of airway obstruction, increased age, or emphysema-type COPD [47]. Similar survival benefits, however, have not been observed in patients with mild to moderate hypoxemia at rest [48,49], hypoxemia during activity only [50], or nocturnal hypoxemia only [46,51,52]. Several small RCTs and observational studies have evaluated the effect of LTOT on short-term measures (6-minute walk test, Borg dyspnea scale, HRQOL questionnaires, and exercise performance) [53] and found conflicting results. Improvements in exercise endurance have been noted with the use of LTOT, but most studies did not show any benefit in overall HRQOL [54,55].

The current Centers for Medicare and Medicaid Services (CMS) approved indications for LTOT are listed in Table 2. In January 2009, NHLBI and CMS launched the largest RCT to date of the effectiveness and safety of LTOT for COPD patients, enrolling 1134 patients and using as the primary outcome death or hospitalization during a 4.5-year follow-up period. The estimated study completion date is May 2013.

Assessment for in-flight use of oxygen during air travel is an important consideration in COPD patients. According to the British Thoracic Society, patients with resting room air SaO₂ > 95% usually do not require oxygen, while patients with resting room air SaO₂ < 92% will likely require supplemental oxygen during flight. Those with values in between will require further testing to determine the need for in-flight oxygen [56]. If the patient is likely to need oxygen and formal testing (hypoxia simulation test) is not available, the current recommendations are to use 2 L of oxygen per minute, or to increase the baseline use of oxygen by 2 L per minute [57,58].

COPD and Sleep

The prevalence of sleep disorders in COPD patients is often underestimated. Age, obesity, and pharmacotherapy (use of hypnotics) may contribute to the underlying sleep disorder, especially sleep apnea [59]. Patients with COPD report frequent sleep problems, including difficulty falling asleep, staying asleep, poor sleep quality, and excessive daytime sleepiness [60].

Obstructive sleep apnea (OSA), defined as increased upper airway resistance during sleep, decreased airflow (hypopnea), and/or complete cessation of flow (apnea) with resultant hypoxemia and arousals, may be co-existent with COPD (overlap syndrome) [61]. The Sleep Heart Health Study (SHHS) [62] and the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA II) [63] concluded that there is no increased risk of OSA in COPD patients, but given the high prevalence of each condition alone, the frequency of the overlap syndrome in the general population may be more than 10%. In a recent prospective observational study, Sharma et al determined that while low FEV₁ did not increase the risk of developing OSA or determine severity of OSA, higher BMI and larger neck circumference (which were more common in patients with COPD) did correlate with

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**Table 2.** Centers for Medicare and Medicaid Services (CMS) Qualifications for Long-Term Oxygen Therapy

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
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| \( P_{O_2} \leq 55 \text{ mm Hg or } SaO_2 \leq 88\% \text{ at rest} \) or \( P_{O_2} \leq 55 \text{ mm Hg or } SaO_2 \leq 88\% \text{ for } \geq 5 \text{ min during sleep for patient with } P_{O_2} \geq 56 \text{ mm Hg or } SaO_2 > 89\% \text{ while awake} \) or \( P_{O_2} \text{ decrease } > 10 \text{ mm Hg or } SaO_2 \text{ decrease } > 5\% \text{ from baseline, for } \geq 5 \text{ min during sleep, with signs/symptoms attributable to hypoxemia} \) or \( P_{O_2} \leq 55 \text{ mm Hg or } SaO_2 \leq 88\% \text{ during exercise for patient with } P_{O_2} \geq 56 \text{ mm Hg or } SaO_2 > 89\% \text{ at rest, provided oxygen improves the hypoxemia that was demonstrated during exercise when patient was breathing room air} \) | \( P_{O_2} \geq 56-59 \text{ mm Hg or } SaO_2 > 89\% \text{ at rest while awake, plus any of the following:} \)

- **Group I**
  - Dependent edema suggestive of congestive heart failure
  - Pulmonary hypertension or cor pulmonale, determined by measurement of pulmonary artery pressure, gated blood pool scan, echocardiogram, or “P” pulmonale on electrocardiogram
  - Polycythemia with hematocrit > 56%
increased risk of OSA [64]. Patients with overlap syndrome have more prolonged nocturnal oxygen desaturation [62], more frequent and more severe pulmonary hypertension [65], worse HRQOL [66], and higher mortality [67,68] than patients with either condition alone. The severity of pulmonary hypertension appears to be related to the degree of hypoxemia, daytime hypercapnia, and reduced FEV\textsubscript{1} [65]. ATS guidelines currently recommend that patients with mild COPD and coexisting pulmonary hypertension be referred for polysomnography [69], as sleep apnea may be contributing to the observed pulmonary hypertension. Additionally, patients with OSA and daytime hypoxemia or hypercapnia should undergo pulmonary function testing to rule out COPD.

Nocturnal continuous positive airway pressure (nCPAP) therapy is currently the standard of care for OSA, and several studies have looked at the benefits of nCPAP in patients with overlap syndrome [68,70,71] (Table 3). Although these are small observational studies, the emerging consensus is that nCPAP may improve survival and reduce the cost of medical treatments for patients with overlap syndrome.

### Table 3. Studies Supporting the Use of Nocturnal Continuous Positive Airway Pressure (nCPAP) in Overlap Syndrome (OS)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients Enrolled</th>
<th>Inclusion Criteria</th>
<th>Findings</th>
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<tr>
<td>Marin et al 2010 [68]</td>
<td>651 (228 with OS treated with nCPAP; 213 with OS not treated with nCPAP; 210 with COPD only; treated with nCPAP)</td>
<td>At least mild OSA (AHI &gt; 5 events/h) COPD with FEV\textsubscript{1} &lt; 80% of predicted</td>
<td>Decreased mortality rate in OS patients treated with nCPAP vs non-treated (31.6% vs 42.2%), with no significant decrease when compared to patients with only COPD treated with nCPAP</td>
</tr>
<tr>
<td>Machado et al 2010 [70]</td>
<td>95 (61 with OS treated with nCPAP and 34 with OS not treated with nCPAP)</td>
<td>Moderate-to-severe OSA (AHI &gt; 15 events/h) COPD with FEV\textsubscript{1} &lt; 80% of predicted and already on LTOT for at least 6 months</td>
<td>Decreased mortality rate in OS treated with nCPAP vs non-treated (19.7% vs 79.4%) at median follow up 41 months</td>
</tr>
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</table>
| Toraldo et al 2010 [71] | 12 (no control group) | Severe OSA (AHI > 30 events/h) COPD with FEV\textsubscript{1} ≤ 50% of predicted with mild hypoxemia and hypercapnia | • \text{PO}_2, \text{PCO}_2, MPAP and AHI improved at 3 months, with no further improvement up to 24 months  
• BMI, daytime sleepiness, nocturnal \text{O}_2 desaturation, and MIP improved at 3 and 12 months, with no further improvement up to 24 months  
• Number of COPD exacerbations and days hospitalized at 2 years decreased |

AHI = apnea/hypopnea index; BMI = body mass index; LTOT = long-term oxygen therapy; MPAP = mean pulmonary arterial pressure; MIP = maximum inspiratory pressure; nCPAP = nocturnal continuous positive airway pressure; OS = overlap syndrome; OSA = obstructive sleep apnea.

### NONINVASIVE POSITIVE PRESSURE VENTILATION

#### Acute Setting

Prognosis of patients with COPD is worse with development of respiratory failure during acute exacerbations. In one study, Hurst et al concluded that the best predictor of acute exacerbations was a history of exacerbations during the previous year [72]. Multiple clinical trials have shown that noninvasive positive pressure ventilation (NIPPV), when added to standard medical therapy, decreased the risk of intubation and in-hospital mortality. Severe hypercapnia and the resultant respiratory acidosis are important predictors of NIPPV treatment failure in the acute setting, with no clear benefits reported when the arterial pH is > 7.35 and usually poor response with a pH < 7.25 [73–75]. In addition to arterial pH, the presence of response within 1 to 2 hours of initiation of NIPPV, defined by both clinical and gas exchange parameters, is a predictor of continued benefit of NIPPV [76]. Decreased efficacy of NIPPV has been noted in the presence of lung infection, decreased level of consciousness, increased respiratory rate, and high initial APACHE (measure of critical illness severity) scores [77]. Among
the contraindications to NIPPV in the acute setting are hemodynamic instability with impending cardiopulmonary arrest, severely decreased level of consciousness, severe agitation, upper gastrointestinal bleed, facial trauma/surgery, and significant airways secretions.

When used in the post-extubation period, NIPPV has a higher chance of reducing the re-intubation and mortality rates, if used early, before overt respiratory failure has developed [78,79].

The use of NIPPV in the acute setting requires a skilled respiratory team and close monitoring of the patient in the appropriate setting.

**Chronic Settings**

In patients with COPD and chronic respiratory failure, the PCO₂ level has only been associated with increased mortality when severe hypercapnia is present (defined as PCO₂ > 55 mm Hg) [80] or when hypercapnia persists after recovery from an acute exacerbation [81]. Use of long-term NIPPV for the management of chronic hypercapnia in patients with COPD is controversial, especially in light of an unclear survival advantage. However, there may be some improvements in subjective dyspnea and HRQOL. As a result, COPD, with chronic hypercapnia, has become one of the major indications for long-term home NIPPV use [82]. Potential mechanisms by which NIPPV improves gas exchange in COPD includes respiratory muscle rest, chemosensitivity restoration, and changes in ventilatory pattern, with increase in tidal volume and minute ventilation, and consequent decrease in respiratory rate. Long-term home NIPPV may be beneficial in reducing dyspnea on exertion and improving lung function, HRQOL, and sleep quality only when used at high intensity (mean inspiratory positive airway pressure (IPAP, 29 mm Hg) as compared with low intensity (mean IPAP 15 mm Hg) [83,84]. NIPPV has also been associated with improved HRQOL and gas exchange when added to pulmonary rehabilitation, compared with pulmonary rehabilitation alone [85,86].

**LUNG VOLUME REDUCTION SURGERY**

The benefits from lung volume reduction surgery (LVRS) are thought to be due to recovery of lung elastic recoil, improvements in diaphragmatic function, and lung–chest wall dynamics. In smaller trials, LVRS decreased dyspnea, improved exercise capacity and HRQOL, and was associated with a reduction in the use of oxygen or corticosteroids [87].

The largest RCT to date that guides current recommendations and selection criteria for LVRS is the National Emphysema Treatment Trial (NETT). Patients found to be at high risk for surgical death (FEV₁ < 20%, associated with either homogenous involvement of the lung, or diffusing capacity of lung for carbon monoxide < 20% of predicted) [88] were excluded early in the trial. For the remainder, those who were randomly assigned to surgery had improved exercise capacity and quality of life, although there was no reduction in mortality in the 2 groups at 29 months. Participants at baseline were stratified according to location of emphysema (based on computed tomography of chest) and exercise capacity into 4 groups: predominantly upper-lobe emphysema and low exercise capacity, predominantly upper-lobe emphysema and high exercise capacity, non–upper-lobe emphysema and low exercise capacity, and non–upper-lobe emphysema and high exercise capacity. Patients in group 1 (predominately upper-lobe emphysema and low exercise capacity at baseline) had significant survival benefit with surgery, while patients in group 4 (non–upper lobe emphysema and high exercise capacity at baseline) had a significantly higher risk of death from surgery compared with medical therapy alone. For patients in groups 2 and 3 there was little difference in the risk of death from surgery. The efficacy of surgery over medical therapy alone therefore depends on the clinical characteristics of the patient selected [89].

**LUNG TRANSPLANTATION**

Lung transplantation (LT) is now a viable therapeutic option for many patients with end-stage lung disease, including COPD. However, it is a procedure not without significant morbidity and mortality. The decision to undergo LT should carefully be weighed against potential risks and benefits to survival and quality of life. Currently, the cumulative 5-year survival for all patients who undergo LT regardless of underlying lung disease is 53%, with slightly better survival for bilateral lung transplant (BLT) vs single lung transplant (SLT)—56% vs 49% [90]. According to the International Society for Heart and Lung Transplantation (ISHLT) registry, from 1995 to 2010, 30,673 people underwent lung transplantation, 34.6% of whom had COPD [90].

The recommended age for LT is less than 55 years for BLT and 60 to 65 years for SLT [91], although most centers make a decision on an individual basis. Other guidelines for selection of patients include severity of disease...
CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Table 4. Disease-Specific Timing for Lung Transplantation in Patients with COPD

<table>
<thead>
<tr>
<th>Selection Criteria</th>
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<tr>
<td>BODE index 7–10 or at least 1 of the following:</td>
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<tr>
<td>History of hospitalization for exacerbation associated with acute hypercapnia (PCO₂ &gt; 50 mm Hg)</td>
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<tr>
<td>Pulmonary hypertension or cor pulmonale, or both, despite LTOT</td>
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<tr>
<td>FEV₁ &lt; 20% and either DLco &lt; 20% or homogenous distribution of emphysema</td>
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BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity; DLco = diffusion capacity of carbon monoxide; FEV₁ = forced expiratory volume in 1 second; LTOT = long-term oxygen therapy. (Adapted with permission from reference [98].)

(based on clinical and physiological criteria), disease not responsive or only partially responsive to medical management, available financial, social and moral support for both peri- and postoperative care, good nutritional status, and absence of significant conditions that would impair rehabilitation [91].

The timing for LT is determined by comparing predictions of post-transplant survival with the estimated survival rate for the underlying lung condition if the disease was allowed to naturally progress (this translates to a mathematical equation with points allotted for various key factors). Interestingly, COPD is the only lung disease for which LT has not been shown to confer significant survival benefits [92,93]. However, several studies demonstrate a significant improvement in HRQOL in all patients after LT [94–97] and a decrease in health care expenditure per life-year gained [95]. Table 4 outlines generally accepted guidelines for consideration for LT in COPD patients according to most recent guidelines from ISHLT [98].

It is recognized that FEV₁ alone is a poor marker of severity of lung disease or need for LT, as it does not reflect the complete lung functional pathology nor does it reflect the systemic involvement from COPD [1,99]. Based on studies that suggest BODE (body weight, airway obstruction, degree of dyspnea and exercise tolerance) is a reasonable estimator of the systemic involvement in COPD [1], guidelines recommend the use of BODE index rather than FEV₁ alone when making listing decisions. A BODE index > 7 is associated with a mortality rate of > 80% at 52 months (less than the expected mortality rate from LT), and a BODE index of < 7 is associated with a survival rate of more than 50% at 5 years (more than the expected survival rate from LT) [1].

When patients are candidates for both LVRS and lung transplantation, the decision is complicated, with no consensus guidelines at present. LVRS is not considered a bridge to transplantation, nor is LT a rescue procedure for failed LVRS. In making this decision, the quality of life and life expectancy for each procedure alone and for LVRS followed by transplantation should be taken into consideration. A recent study by Nathan et al did not show significant differences in the mortality rate at 1 month, post-transplant hospital stay, and 12-month survival rate between transplant patients with and without prior LVRS [100], suggesting that LVRS is not a contraindication for future LT.

CONCLUSION

In conclusion, the care of patients with COPD requires a multidisciplinary approach that involves not only pharmacologic therapies but also meticulous attention to the physical, social, and psychological well being of the individual. An individualized prescription of nonpharmacologic therapies is necessary to address the systemic disease that is COPD. More research is needed in identifying the individual elements of such therapies that would garner the most success in reducing the health and economic burdens of COPD.

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