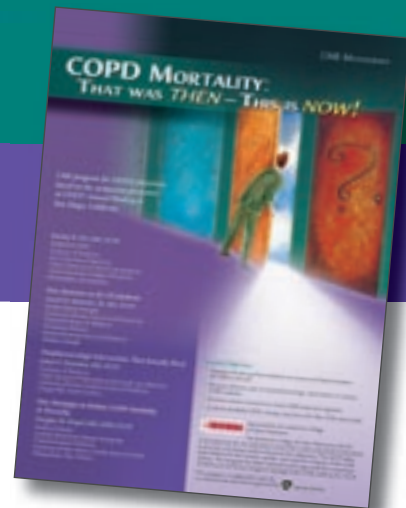


COPD MORTALITY: THAT WAS *THEN* – THIS IS *NOW!*

**CME PROGRAM FOR CLINICIANS WHO TREAT COPD,
BASED ON A LIVE SYMPOSIUM**

Earn CME credit using this monograph

COPD MORTALITY: THAT WAS *THEN*—THIS IS *NOW!*



Dear Doctor:

The overwhelming and positive feedback to a recent symposium on COPD (chronic obstructive pulmonary disease) has prompted us to make this program available to those who did not attend the symposium.

The CME program addresses clinical issues in the treatment of COPD. A post-test is at the conclusion of the monograph and must be completed in order to earn 1.5 hours of CME credit; this can be submitted via fax or via the website <http://www.chestnet-cme.org/copd.htm>. I know you will find it interesting and relevant for your medical practice.

Sincerely,

A handwritten signature in black ink, appearing to read "Stanley B. Fiel".

Stanley B. Fiel, MD

Symposium Chair

Professor and Chief

Division of Pulmonary/Critical Care Medicine

Drexel University College of Medicine

Philadelphia, Pennsylvania



Sponsored by the American College of Chest Physicians.

The American College of Chest Physicians (ACCP) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The ACCP takes responsibility for the content, quality, and scientific integrity of this CME activity. This program has been reviewed and is approved for a maximum of 1.5 hours of clinical category I (preapproved) CME credit by the ACCP.

This program is supported in part by an unrestricted educational grant from  GlaxoSmithKline

COPD MORTALITY: THAT WAS *THEN* – THIS IS *NOW!*

CME program for clinicians who treat COPD based on the symposium presented at the CHEST Annual Meeting in San Diego, California

Stanley B. Fiel, MD, FCCP

Symposium Chair
Professor and Chief
Division of Pulmonary/Critical Care Medicine
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Philadelphia, Pennsylvania

New Statistics on the US Epidemic

David M. Mannino, III, MD, FCCP

Medical Epidemiologist
Centers for Disease Control and Prevention
Clinical Professor of Medicine
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Nonpharmacologic Interventions: Which Actually Work?

James F. Donohue, MD, FCCP

Professor of Medicine
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New Strategies to Reduce COPD Morbidity

& Mortality

Douglas W. Mapel, MD, MPH, FCCP

Medical Director
Lovelace Clinic Foundation
Clinical Assistant Professor
University of New Mexico Health Sciences Center
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LEARNING OBJECTIVES

- Appraise the driving forces behind the current and future burdens of COPD in the United States.
- Illustrate effective uses of nonpharmacologic interventions in various COPD patients.
- Examine current literature on many COPD treatment regimens.
- Contrast available COPD therapy outcomes with that of the recent past.



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COPD MORTALITY: THAT WAS *THEN* – THIS IS *NOW!*



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Douglas W. Mapel, MD, MPH, FCCP has disclosed a relationship with the following corporate organization: Consultant and Grants/Research Support - GlaxoSmithKline.

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NEW STATISTICS ON THE US EPIDEMIC

COPD – Ill Defined and Often Overlooked

Chronic obstructive pulmonary disease (COPD), acknowledged as the fourth leading cause of death in the United States,¹ is a group of diseases characterized by airflow obstruction and associated with breathing-related symptoms such as chronic cough, exertional dyspnea, and mucus hypersecretion.^{2,3} Because of its multiple symptom complex, a true diagnosis of COPD can be problematic. An estimated 10 million US adults reported physician-diagnosed COPD in 2000.² However, data from the third National Health and Nutrition Examination Survey (NHANES III) estimate that 24 million US adults have evidence of impaired lung function, indicating that COPD is substantially underdiagnosed.⁴ To avoid misdiagnosis, the defining characteristics of COPD should be better identified.

Defining COPD: Establishing a GOLD Standard

Definitions of COPD have varied temporally and between different organizations. Traditionally diagnosed on the basis of patient-reported symptoms,^{5,6} a definitive diagnosis is confounded by symptom overlap.

AMERICAN THORACIC SOCIETY. The 1995 American Thoracic Society (ATS) guidelines define COPD as the presence of airway obstruction,⁵ a focus that makes this disease complex indistinguishable from asthma or other obstructive diseases. Descriptions such as airway obstruction and partial reversibility also characterize asthma; and chronic bronchitis and emphysema are also generally progressive and may be accompanied by the airway hyperreactivity that can indirectly lead to infections and alveolar damage (Table 1). The table conveys symptom overlap and disease continuum and progression, and suggests, as the ATS guidelines state, that “the obstruction in many patients with COPD may include a significant reversible component, and that some patients with asthma may go

TABLE 1

THE OBSTRUCTIVE LUNG DISEASES: A CONTINUUM OF OVERLAPPING CHARACTERISTICS.

	Reversibility	Sputum infections	Alveolar damage
Asthma	++++	—	—
Chronic bronchitis	++	+++	+
Chronic bronchitis & emphysema	+	++	+++
Emphysema	—	+	++++

Adapted from Turner-Stokes L, Turner-Warwick M. Thoracic manifestations of multisystem diseases. In Baum GL, Wolinsky E, Eds. *Textbook of Pulmonary Diseases*. Boston, MA: Little Brown and Co;1989.

on to develop irreversible airflow obstruction indistinguishable from COPD.”⁵

The ATS guidelines define chronic bronchitis as the presence of chronic productive cough for 3 months in each of two successive years.⁵ Wheezy bronchitis is an archaic (and now obsolete) British term for pediatric patients who develop wheezing with respiratory infections and then tend to “grow out of it” as teenagers and adults—a kind of time-lapse reversibility.

The ATS guidelines state that “the obstruction in many patients with COPD may include a significant reversible component, and that some patients with asthma may go on to develop irreversible airflow obstruction indistinguishable from COPD.”

Emphysema, defined anatomically, is the permanent abnormal airspace enlargement that occurs near the terminal bronchioles and is accompanied by destruction of the alveolar walls.⁵

BRITISH THORACIC SOCIETY. In 1997 the Standards of Care Committee of the British Thoracic Society (BTS) defined COPD as a general term subsuming chronic bronchitis, emphysema, chronic obstructive airways disease, chronic airflow limitation, and some cases of chronic asthma as different aspects of the same problem and “diagnostic labels encompassed by COPD.”⁷

In their summary of treatment guidelines, the BTS committee proposed spirometry as the only objective measurement indicative of COPD, stating that symptoms such as breathlessness, wheeze, and cough are only suggestive. Positing a spirometric definition, the BTS committee established a forced expiratory volume produced in 1 second (FEV₁) of <80% of predicted and a forced vital capacity (FEV₁/FVC) ratio of <70% as confirmation of airways obstruction that does not change markedly over time, but which is partially reversible by bronchodilator or other therapy.⁷

COLLABORATION STRIKES GOLD. In 2000, The Global Initiative for Chronic Obstructive Lung Disease (GOLD), an international collaborative effort of the National Heart, Lung, and Blood Institute and the World Health Organization, published a workshop report which established the current definition of COPD.

The GOLD Guidelines define COPD as “a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.” The GOLD investigators affirmed that spirometric measurement—a physiologic definition—should serve as the gold standard for diagnosis and assessment of COPD, in that spirometry is the most standardized, objective, and reproducible way to measure airflow limitation.⁸

Classifying Severity: GOLD Stages of COPD

For educational purposes, The GOLD Guidelines recommended a simple classification of disease severity into four stages based on airflow limitation as measured by spirometry (Table 2). This staging, which is essential for diagnosis, also provides a useful description of the severity of pathologic changes in COPD. Specific FEV₁ cut-points are used for purposes of simplicity, as these

TABLE 2

GOLD GUIDELINES: CLASSIFICATION OF SEVERITY.

Stage	Characteristics
0: At risk	Normal spirometry Chronic symptoms (cough, sputum)
I: Mild	FEV ₁ /FVC <70% FEV ₁ ≥80% of predicted With or without symptoms (cough, sputum)
II: Moderate	FEV ₁ /FVC <70% Stage IIA: FEV ₁ 50%–80% of predicted Stage IIB: FEV ₁ 30%–50% of predicted With or without chronic symptoms (cough, sputum, dyspnea)
III: Severe	FEV ₁ /FVC <70% FEV ₁ <30% of predicted or FEV ₁ <50% of predicted plus respiratory failure or clinical signs of cor pulmonale

Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. NHLBI/WHO Workshop Report; March 2001. Available at www.goldcopd.com/workshop.html. Accessed February 2003.

cut-points have not been clinically validated. Nevertheless, the GOLD criteria for mild (Stage I) COPD are an FEV₁/FVC ratio of <70% and FEV₁ ≥80% of predicted. Moderate (Stage II) COPD encompasses a wide range of FEV₁ values,^{2,8,9} reflecting the impact of airflow obstruction on symptom severity and disease-related disability; therefore, Stage II COPD is divided into two stages (Stages IIA and IIB) for the purposes of management.

The Burden of COPD

The GOLD Workshop Report states that, according to available COPD prevalence and morbidity data, the disease is greatly under-recognized and not generally diagnosed until it is clinically apparent and moderately advanced.⁸ Mortality data also underestimate COPD as a cause of death because it is more likely to be cited as contributory rather than as an underlying cause.^{8,10}

Overall Increased Mortality

Figure 1 dramatically illustrates that COPD is not only the fourth leading cause of death in the United States, but is also the only one of the top four or five leading causes of death that has increased over the past 30 years (+163%). The various cardiovascular diseases have shown declines in mortality rates of 35% to 64%.² And in 2000, for the first time, the number of women dying of COPD surpassed the number of men: 59,936 versus 59,118.² These numbers represent an average rate of 82.6 deaths per 100,000 men, and 56.7 per 100,000 women in 2000^{2,11}—up from respective rates of 73.0 and 20.1 in 1980. Calculations are based upon designations set forth in the *International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM)*, for data gathered through 1998; the ICD-10 designation, used from 1999 onward, applies the terms “chronic lower respiratory disease” and “COPD and allied conditions” to describe the diseases encompassed by COPD (ICD-9 codes 490-496 and ICD-10 codes J42-J46).^{8,11}

COPD Prevalence, Self-Reported and Otherwise

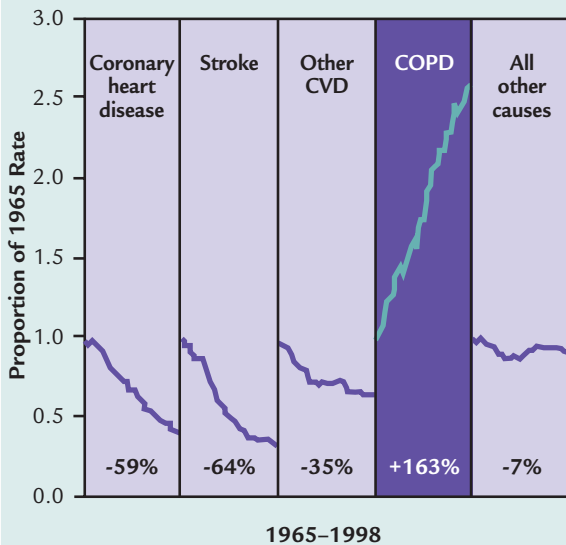
The CDC’s *Morbidity and Mortality Weekly Report (MMWR)* of August 2, 2002 summarized trends in COPD measures

(self-reported, physician-determined, objectively determined) during 1971–2000.² Whites had statistically significant ($P < 0.05$) higher rates of COPD than blacks for 1984, 1986, and 1994.² When stratified by age group, a statistically significant ($P < 0.05$) decrease occurred in moderate COPD in individuals 25–54 years of age but not among other groups; when stratified by race, a similar decrease occurred among blacks, but not among whites.²

**The Changing Face of COPD:
A Dangerous Trajectory for Women**

Since 1987, women have had higher rates of self-reported COPD than men, and during 1980–1996, the trend for COPD increased for women but not for men.² Data from NHANES I^{12,13} and NHANES III⁴ estimated the prevalence of COPD on the basis of spirometric definitions. For both mild and moderate COPD, prevalence was higher among men than women and increased with increasing age. However, from NHANES I (1971–1975) to NHANES III (1988–1994), the prevalence of moderate COPD decreased among men but not among women.² This is a most dangerous trajectory. Although only current through 1996, the age-adjusted death rates per 100,000 population show a threefold increase in women for 1980–1996.⁸ Moreover, since 1989, hospitalizations for COPD have also increased, with elimination of the difference in hospitalization rates between men and women: 322,000 men and 404,000 women were hospitalized for COPD in 2000.² These increasing trends in COPD hospitalizations and mortality among women probably reflect increased smoking in women since the 1940s, relative to men.¹⁴

FIGURE 1
Percent change in adjusted US death rates, 1965–1998.



Adapted from Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. NHLBI/WHO Workshop Report; March 2001. Available at www.goldcopd.com/workshop.html. Accessed February 2003.

...the age-adjusted death rates per 100,000 population show a threefold increase in women for 1980–1996.

COPD Hospitalizations

In 2000 there were 8 million outpatient hospital visits for COPD in the United States, and 1.5 million emergency room visits. In that year, 726,000 hospital admissions were attributed to COPD, which constitutes approximately 2% of all hospitalizations. If these numbers are recalculated so that COPD is named as either the main or a contributing cause of hospitalization in adults age 25 and older, then the rate climbs to 7% of all hospitalizations for 2000, or an additional 2.5 million. And if this definition is further restricted to include adults age 45 or older with COPD as the underlying or contributory



cause, this amounts to 20% of all hospitalizations. Since 1990, hospitalizations for COPD have increased among all age groups, with the largest increases seen in individuals 65–74 years of age (62%) and older (≥75 years: 52%).²

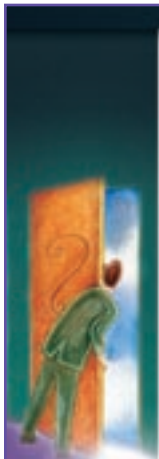
Fewer Years in Their Lives, Less Life in Their Years

Adults with COPD experience activity limitation about twice as often as adults without COPD.² In assessments conducted by NHANES III⁴ during 1991 through 1994, 34.2% of individuals with self-reported COPD claimed difficulty in walking ¼ mile, compared to 11.2% of subjects with this complaint who did not believe they had COPD. In addition, 30.5% of those with self-reported COPD had difficulty lifting or carrying 10 pounds, compared to 9.5% of those who did not claim to have COPD.

COPD is currently the eighth leading cause of disability-adjusted life-years (DALYs) in American men, and the seventh leading cause of DALYs in American women. From an international standpoint, COPD is expected to be the fifth leading cause of DALYs in 2020—clearly a grim prediction.

A Costly Disease

Negative effect on quality of life notwithstanding, COPD is a costly disease. Direct medical costs of COPD in the United States in 1993 averaged \$14 billion. Similarly, the estimated indirect costs of COPD in 1993 were \$9.2 billion. In stark contrast, in that same year, the combined direct and indirect costs of managing asthma totaled \$12.6 billion.



CONCLUSION: QUELLING THE EPIDEMIC

Although there have been considerable gains in terms of tobacco-control programs and other efforts to protect respiratory health, COPD remains a major cause of morbidity, mortality, and disability in the United States. Asthma, respiratory infections, and exposure to ambient pollutants in the home and workplace are also risk factors for the development and progression of COPD,^{2,15-18} and COPD itself is a risk factor for lung cancer¹⁹ or contributory to early death due to other causes. The continuing increase in COPD hospitalizations among men and women, and the rise in COPD deaths among women, highlight a critical need for both clinical and public health interventions.

Persons with COPD, not knowing they have the disease, generally deny or underestimate the extent to which their daily activities are limited. In the absence of spirometry, a visit to the doctor may prove futile because COPD symptoms are often silent, hence not recognized and not diagnosed. To avoid misdiagnosis, the defining characteristics of COPD should be identified via spirometry, which has been firmly established as the gold standard for the diagnosis of COPD.

Persons with COPD, not knowing they have the disease, generally deny or underestimate the extent to which their daily activities are limited.

Early detection might alter the course and prognosis of COPD. The National Lung Health Education Program, or NLHEP, is a program that seeks to involve primary-care physicians in the early identification and treatment of obstructive lung disease.²⁰ This initiative, along with greater attention paid to more accurate differential diagnosis, may have a positive effect on both case-by-case and large-scale COPD management.

NONPHARMACOLOGIC INTERVENTIONS: WHICH ACTUALLY WORK?



Optimizing Care

In addition to the new medications recently added to the pulmonologist's armamentarium, a great deal is being learned regarding other aspects of care of the COPD patient. This section provides an overview of the nonpharmacologic interventions currently employed in the management of COPD, which are directed at many of the challenges that physicians and COPD patients alike may encounter in the face of this progressive and debilitating disease.

Treatment Considerations

COPD and "The Emotional Straitjacket"

COPD is a progressive, debilitating disease. As it progresses in severity over time, many patients with COPD will encounter great physical and psychosocial losses. Many COPD patients are said to live in an "emotional straitjacket", characterized by a unique pattern of low self-esteem, feelings of helplessness and worthlessness, and a lack of self-confidence and spontaneity.²¹ They feel unable to vent their emotions for fear of affecting their breathing.

As it progresses in severity over time, many patients with COPD will encounter great physical and psychosocial losses.

Psychosocial factors—individual traits and social supports that allow either coping with or adapting to one's environment—combined with the patient's own coping skills, are important in determining a patient's psychological response to COPD.²² A patient who lacks coping skills or social support can oftentimes develop depression or anxiety.

DEPRESSION. Compared with the general population, the prevalence of depression is

more common in those patients with physical illness. Depression has been reported in 5% to 10% of primary care patients, and in 10% to 14% of hospital inpatients.²³ According to the International Classification of Mental and Behavioral Disorders (ICD-10) criteria (Table 3), a major depressive episode is defined as the presence of at least two core symptoms and some frequently associated symptoms for a minimum of 2 weeks.²⁴

However, it should be noted that prevalence rates for depression are reported to vary widely among the physically ill. The reported prevalence of depression in COPD varies greatly among studies; however, it is likely that around 21% of COPD outpatients suffer from depression.²⁵

A number of factors may explain these fluctuations in prevalence rates. In some patients with comorbid illness, anxiety, distress and motor agitation may be more prominent than

TABLE 3
ICD-10 CRITERIA FOR DIAGNOSIS OF DEPRESSION.

Core symptoms	Associated symptoms
Depressed mood	Poor concentration and attention span
Loss of interest and enjoyment in life	Low self-esteem and self-confidence
Loss of energy, fatigued easily	Ideas of guilt and worthlessness
Reduction of activity – marked tiredness after trivial effort	Bleak and pessimistic views of the future
Acts of self-harm or suicide	Disturbed sleep
	Anorexia

Adapted from *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Description and Diagnostic Guidelines*. Geneva, Switzerland: World Health Organization, 1992.

depressive symptoms at times. In other patients, depressive symptoms may sometimes be clouded by irritability, excessive alcohol use, exacerbation of pre-existing phobic or obsessive behaviors, or hypochondria.²⁶

ANXIETY AND PANIC. According to ICD-10 criteria, the primary feature of a generalized anxiety disorder is generalized, persistent anxiety that is not restricted to any particular purpose.²⁴ Symptoms of anxiety are usually chronic, yet fluctuate, and be present for most days for weeks or months at a time. Anxiety, if left unabated, can lead to panic disorder, which is characterized by severe, unpredictable attacks of anxiety.

Anxiety and panic share a complicated connection with respiratory disease. Dyspnea and hyperventilation are strong indicators of anxiety, and are also considered to be core features of panic attacks.²⁷ The consequences of hyperventilation include reduced PaCO₂, respiratory alkalosis, and a wide array of psychiatric symptoms not unlike those seen in anxiety.²⁸

A number of theories have emerged to explain the correlation between anxiety, panic, and dyspnea. The Hyperventilation Model, proposed by Smoller and associates,²⁹ maintains that hyperventilation is responsible for both dyspnea and panic. Another model, the CO₂ Hypersensitivity/False Alarm model,³⁰⁻³² suggests that hypersensitivity of the medullary chemoreceptors to CO₂ produces both panic and dyspnea and panic, resulting in hyperventilation. Yet another theory, the Cognitive-Behavioral Model, asserts that panic is the response to the fear and misinterpreted physical sensations associated with dyspnea and hyperventilation.³³⁻³⁵ Although all these models appear to be valid, none completely explains the interaction between mood and respiration.

DIAGNOSIS. Anxiety and depression have been found to predict functional status and quality of life in COPD better than lung function and exercise tolerance.²⁶ Thus, diagnosis and adequate treatment of these mood disorders is as important as the use of pharmacologic agents (e.g., bronchodilators) in managing COPD.

A major challenge in detecting depression lies in differentiating it from other mood disorders that have similar symptoms, such as dysthymia, somatic syndrome, and adjustment disorder associated with physical disease. Another challenge is distinguishing whether somatic symptoms (e.g., fatigue, weight loss, sleep loss) are due to depression, physical illness, or a combination of both.

The structured psychiatric interview remains the gold standard for diagnosis of depression. A number of self-administered questionnaires are also available for detecting depression; these include the Center for Epidemiological Studies–Depression Scale (CES-D), the Zung Depression Scale, the Beck Depression Inventory (BDI), the Geriatric Depression Scale (GDS), and the Hospital Anxiety and Depression Scale (HAD). Of these questionnaires, only the HAD Scale has been developed specifically for use in physically ill patients. Although useful for screening purposes and easy to administer, the HAD significantly overdiagnosed affective disorder in COPD patients when compared with structured psychiatric interview.²⁶

TACTICS FOR MANAGING MOOD DISORDERS. The management of comorbid affective disorders in COPD patients can be challenging. It is difficult to undertake studies of adequate duration in patients who have two disorders, both of which fluctuate, sometimes together but sometimes independently (as when COPD patients have acute exacerbations), especially when one of the disorders (COPD) is gradually increasing in severity.²⁶

Cognitive and behavioral psychotherapy have been found to increase the COPD patient's "self-efficacy" by helping enhance the patient's own psychosocial assets and coping skills.²⁶ The behavioral techniques are designed to reinforce adherence to lifestyle changes, including exercise and smoking cessation, and to help patients manage their symptoms. Cognitive coping techniques help make the patient aware of negative feelings and substitute positive ones for them. A number of studies have reported that cognitive and behavioral techniques helped improve exercise tolerance and dyspnea.^{37,38}

Behavioral techniques are designed to reinforce adherence to lifestyle changes, including exercise and smoking cessation, and to help patients manage their symptoms.

Although there have been individual successes, neither aerobic exercise,^{39,40} progressive muscle relaxation,⁴¹ stress management,⁴² nor education on their own has produced demonstrable, large-scale effects on either anxiety or depression in patients with COPD.⁴³⁻⁴⁵ However, as part of a comprehensive pulmonary rehabilitation program, these psychological therapies may have some value. Larger studies are needed to validate these types of interventions.

COPD and Sleep

In the past 30 years it has been discovered that sleep in COPD patients can be a challenging and stressful time rather than a period of rest. Despite the complex neural mechanisms that control the act of breathing, all COPD patients become more hypoxemic during sleep than awake,⁴⁶ and many COPD patients, particularly those in Stages IIB and III, develop respiratory failure during sleep. There is also considerable overlap in some patients with chronic bronchitis and obstructive sleep apnea syndrome (OSAS).

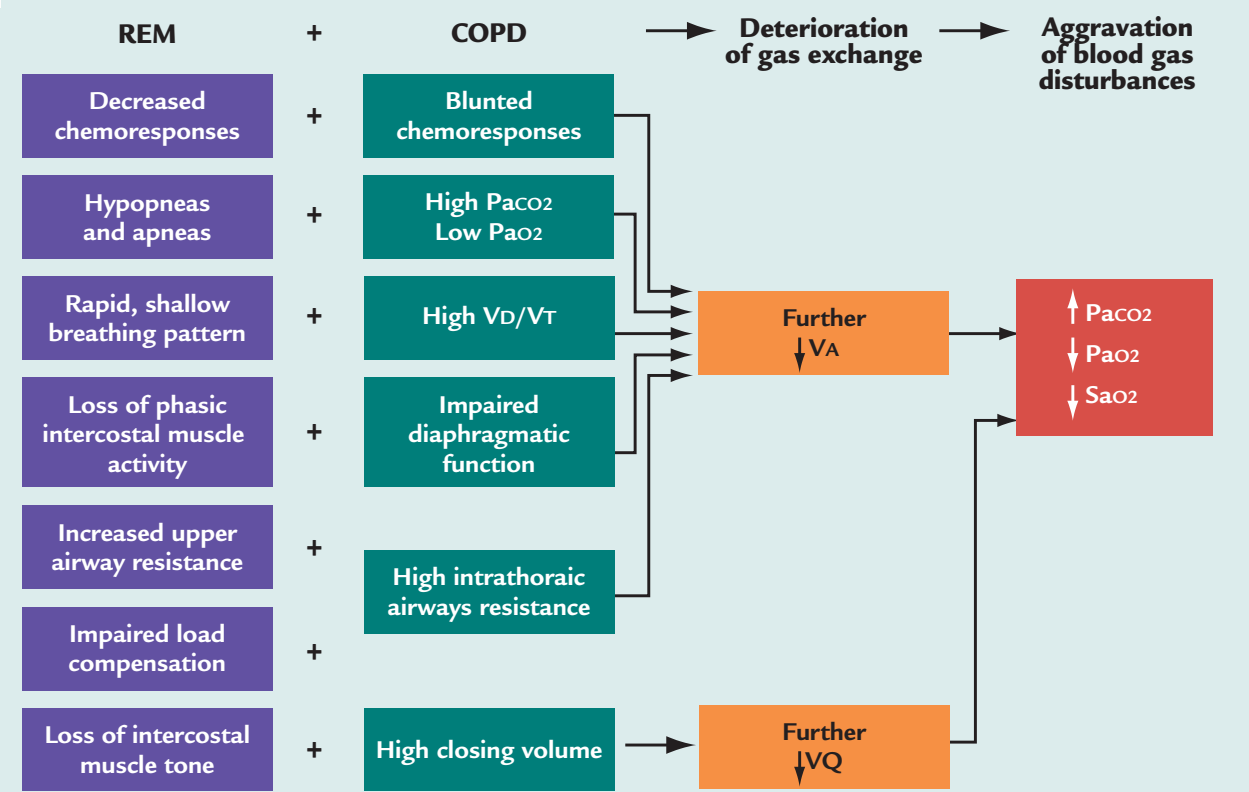
NOCTURNAL HYPOXEMIA. Severe hypoxemia has been described during REM sleep, which occurs on average at 90-minute intervals throughout the night. The duration of each REM episode increases from the beginning to the end of the night. The most severe episodes of nocturnal hypoxemia occur during phasic REM sleep (during rapid eye movements).⁴⁷

Dardes and colleagues⁴⁸ noted four patterns of continuous monitoring of night oximetry in patients with COPD:

- Type I: the pink puffer with stable SaO_2 , with a couple of desaturation episodes (<4%)
- Type II were 2-4 episodes per night with very slow (4%-20%) falls of SaO_2 , seen mostly in blue bloaters
- Type III contained very frequent and chaotic fluctuations of SaO_2 , seen in overlap syndrome (OSAS + COPD)
- Type IV combined slow falls with chaotic fluctuations of SaO_2 , seen in overlap syndrome

REM SLEEP AND COPD PATHOPHYSIOLOGY. As shown in Figure 2,⁴⁹ there is a profound interaction between the sleep state and COPD that can lead to nocturnal oxygen desaturation (NOD) and hypoxemia. The consequences of this interaction include: increased

FIGURE 2
REM sleep and COPD pathophysiology.



V_D=volume of dead space; V_T=tidal volume; V_A=alveolar ventilation; V_Q=ventilation-perfusion ratio.
Adapted from Phillipson EA. *Chest*. 1984; 85(6 Suppl):24S-30S.



pulmonary arterial pressure and pulmonary arterial hypertension, cardiac arrhythmias, polycythemia, and poor sleep quality (including daytime sleepiness).

DIAGNOSIS. Although this procedure is unlikely to be performed in all COPD patients, the importance of sleep studies (polysomnography) in a select group of patients with COPD cannot be overstated. Major indications include those patients with suspected nocturnal hypoxemia, including those who develop hypoxemic complications such as cor pulmonale and polycythemia despite reasonable daytime Pao₂ levels (>60 mm Hg), and those patients suspected of having OSAS or overlap syndrome (Table 4).⁵⁰

TABLE 4

INDICATIONS FOR POLYSOMNOGRAPHY STUDIES IN COPD.

- **Patients with hypoxemic conditions despite daytime Pao₂ >55 mm Hg**
 - Pulmonary hypertension
 - Cor pulmonale
 - Polycythemia
- **Patients with suspected OSAS or overlap syndrome**
- **Patients with excessive nocturnal hypoxemia**
 - >30% of total time in bed spent below 90% of oxygen saturation
 - A drop in oxygen saturation below baseline of 90% for longer than 5 minutes, reaching a nadir of 85% or lower
- **Titration of nocturnal oxygen therapy (e.g., CPAP, NPPV) in patients with sleep-related breathing disorders**

Because of the cost of performing full-night polysomnography, less detailed studies (e.g., overnight oximetry) can be performed in cases where no additional risk to the patient is present. OSAS can also be evaluated by investigating patient history of snoring, excessive daytime sleepiness, and witnessed apneas.

MANAGEMENT. Long-term oxygen is considered the only measure shown to decrease nocturnal hypoxemia and mortality in this patient population.^{51,52} The current recommendations by the American Thoracic Society are to increase daytime oxygen requirements at rest by 1L/min during exercise and sleep in those patients that fulfill the requirements for supplemental oxygen.⁵ Continuous Positive Airway Pressure (CPAP) has been found to be effective for those with OSAS or overlap syndrome.⁵³

The device for delivering nocturnal oxygen therapy does not seem to matter as much as the need for careful monitoring of the patient in order to prevent any further CO₂ retention. Thus, there is a need for careful oxygen titration and adequate follow-up using arterial blood gas sampling.

...the importance of sleep studies (polysomnography) in a select group of patients with COPD cannot be overstated.

Nutrition in COPD

About one in four COPD patients are unable to maintain good nutrition, as indicated by weight loss. In patients hospitalized for exacerbations, this number can grow as high as 50%.^{54,55}

WEIGHT LOSS AND SURVIVAL. There is a negative correlation between weight loss and survival in COPD. A loss of protein and lean body mass can lead to skeletal muscle and diaphragmatic weakness, and ultimately impairment in daily functioning and quality of life. Several studies have shown that a low body mass index (BMI), defined as <18 kg/m², is associated with an increased mortality risk.^{54,56}

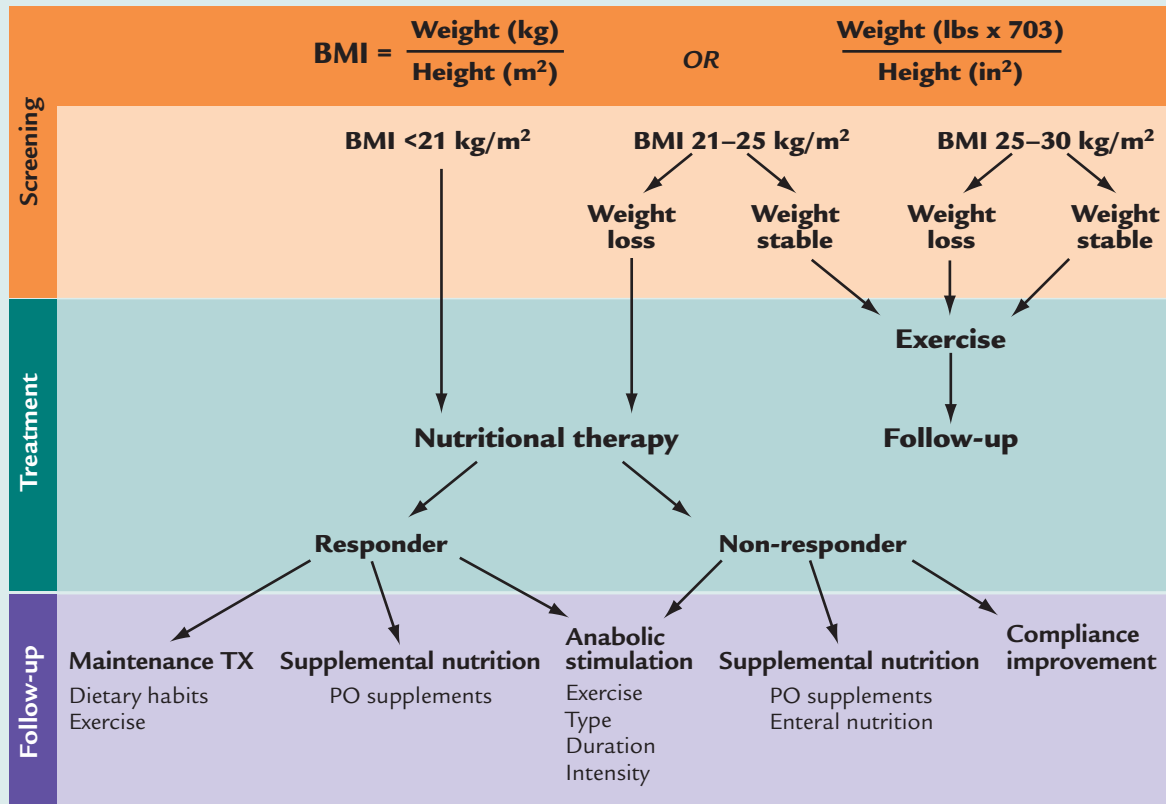
Although the exact cause of weight loss is not always known, factors may include poor appetite, high resting energy expenditure, and desaturation during eating. The development of airflow limitation is related to oxidative stress, which may be due in part to a dietary deficiency of antioxidants; hence dietary supplementation may also be a beneficial therapeutic intervention.

OPTIMIZING NUTRITIONAL SUPPORT. Figure 3 presents a practical approach to nutritional screening and treatment.⁵⁷ Screening should take into account maintaining an ideal body weight (BMI 24 kg/m²) as well as evaluating the presence or absence of involuntary weight loss.

If a patient is underweight (BMI <18 kg/m²), nutritional supplementation is indicated. Involuntary weight loss in patients with a BMI <25 kg/m² should also be treated to avoid further deterioration. Patients with BMI >25 kg/m² should be monitored if involuntary weight loss is detected in order to insure that the weight loss does not become progressive. If possible, measurement of fat-free mass should also be implemented, since this allows identification of normal-weight patients with depleted fat-free mass and respiratory muscle strength.

FIGURE 3

Nutritional screening and therapy.



BMI=body mass index
 Schols AMWJ, Wouters EFM. Nutritional assessment and support of the COPD patient. In Similowski T, Whitelaw WA, Derenne J-P, eds. *Clinical Management of Chronic Obstructive Pulmonary Disease*. New York, NY: Marcel Dekker Inc;2002:681-701.

If a patient is underweight (BMI <18 kg/m²), nutritional supplementation is indicated.

Attempts should be made to restore nutritional balance. Several smaller meals a day may help maintain caloric needs and avoid undue dyspnea. Switching to a diet emphasizing fats rather than carbohydrates may not only increase caloric intake per unit volume, but may also reduce ventilatory workload,⁵⁸ since a fat-concentrated diet metabolizes to less CO₂ than one rich in carbohydrates. The role of hormonal therapy such as growth hormones is controversial in COPD.



The Role of Nonpharmacologic Tactics

Respiratory Physiotherapy

TRADITIONAL TECHNIQUES. Mucociliary clearance is often severely impaired in patients with COPD. The quantity of secretions can range from 10–100 mL/24 hours,⁵⁹ but this amount can triple with exacerbations. Decreased mucus clearance can contribute to infection and narrow airways, which increase airflow resistance and work of breathing.

For over a century, physiotherapists have employed a number of techniques designed to mobilize and clear secretions from the central airways, thereby optimizing breathing performance and efficiency. There is no question that in some patient populations (e.g., cystic fibrosis) these techniques can have a positive impact on the quality of life for some patients. However, in the case of COPD it is hard to assess the effectiveness of secretion mobilization and removal techniques due to the small sample sizes that some studies used and the lack of control groups.

SECRETION REMOVAL/MOBILIZATION. Literature reviews have shown that coughing and forced expiratory techniques (FET) clear secretions from central airways.^{60,61}

Mobilization techniques include postural drainage, percussion, vibration, and shaking techniques, the positive expiratory pressure (PEP) mask, and high frequency oscillators. While it appears that postural drainage may be an effective adjunct to coughing and FET in assisting secretion clearance from the central or peripheral airways in patients with excessive secretions, other techniques such as percussion, vibration and shaking cannot be proven. Many if not most patients with COPD do not produce large amounts of sputum, and will not require traditional chest physiotherapy.⁶²

PURSED LIP BREATHING. Breathing exercises, such as pursed lip breathing and other diaphragmatic type of breathing techniques, are directed at symptom relief. Although there may have been some patients who have benefited, these techniques, when looked at rigorously, do not alter ventilation or improve the efficiency of breathing, and their ability to decrease dyspnea is questionable.

Exercise

Individuals are grossly deconditioned, particularly those who are in advanced stages of the disease. This is primarily due in response to dyspnea. There is no doubt that exercise training, especially in sedentary COPD patients, improves physical performance and health-related qual-

ity of life.⁶³ The beneficial effects from exercise training on dyspnea appears to exceed those attained from either bronchodilator or oxygen therapy.⁶⁴ An exercise training program must include systematic exercises of muscles that the patient will use in everyday activities, such as walking and arm motion. Upper arm training is especially important, since arm activity can produce unusual dyspnea because of competition with accessory respiratory muscles.

An exercise training program must include systematic exercises of muscles that the patient will use in everyday activities, such as walking and arm motion.

Respiratory Muscle Training

Respiratory muscle training (RMT) remains a controversial treatment modality in COPD. The mechanisms by which RMT can improve exercise tolerance in COPD are not understood. It is hypothesized that a reduction in breathlessness, secondary to improvements in respiratory muscle strength,^{65–68} improves exercise tolerance.

Oxygen

ROLE IN OVERALL MANAGEMENT. Oxygen is well established as a nonpharmacologic intervention that has a positive effect on outcome. As shown in Table 5,⁶⁹ the deleterious effects of chronic hypoxemia can be ameliorated by the administration of long-term oxygen therapy (LTOT) ≥ 15 hours/day.⁵² Another benefit of oxygen therapy is the improved survival rates at 1 year and 3 years.

Oxygen is prescribed and reimbursed based on arterial blood gas evidence of hypoxemia. Patients with a $PaO_2 \leq 55$ mm Hg at rest should receive LTOT.^{51,52} If the PaO_2 is between 56 and 59 mm Hg and there are signs of cor pulmonale, the patient should receive LTOT. Oxygen is generally not prescribed for patients whose PaO_2 exceeds 60 mm Hg unless desaturation occurs during sleep or exertion.

Based on the principles cited in Table 6,⁵ oxygen therapy is prescribed to ensure that oxygen is continuously provided at a level that alleviates hypoxemia ($PaO_2 > 60$ mm Hg), which generally corresponds to an arterial oxygen saturation (SaO_2) $> 90\%$. When prescribed for home use, an oxygen prescription should indicate: (1) the oxygen dose (L/min), (2) the number of hours per day that oxygen therapy is required, (3) the dose required during exercise, (4) the oxygen supply system: concentrator, compressed gas cylinder, or liquid oxygen reservoir,

TABLE 5

LONG-TERM OXYGEN THERAPY: IMPACT OF CHRONIC HYPOXEMIA.

Deleterious effects of chronic hypoxemia (PaO ₂ ≤55 mm Hg)	Beneficial effects of long-term oxygen therapy (≥15 hours/day)
Life expectancy	
Poor survival	Improved survival
Quality of life	
Poor exercise performance	Improved exercise performance
Increased hospital demand	Reduced hospitalization
Neuropsychological disturbance	Improved neuropsychological status
Physiological effects	
Reduced oxygen transport and delivery	Improved oxygen transport and delivery
Development of polycythemia	Reduction (but rarely correction) of polycythemia
Cardiac arrhythmias during sleep	Marked improvement of cardiac arrhythmias during sleep
Pulmonary circulation	
Development and worsening of pulmonary hypertension	Progression of pulmonary hypertension is reversed or stabilized or attenuated

Weitzenblum E, et al. Long-term oxygen therapy in stable COPD. In Similowski T, Whitelaw WA, Derenne J-P, eds. *Clinical Management of Chronic Obstructive Pulmonary Disease*. New York, NY: Marcel Dekker Inc;2002:781-812.

TABLE 6

LONG-TERM OXYGEN THERAPY: GUIDELINES.

Indications	Treatment goals
Absolute	
PaO ₂ ≤55 mm Hg or SaO ₂ ≤88%	PaO ₂ ≥60 mm Hg or SaO ₂ ≥90%; Appropriately adjusted O ₂ dose during sleep and exercise
In patients with cor pulmonale	
PaO ₂ 55–59 mm Hg or SaO ₂ ≥89%	Same as above
ECG evidence of cor pulmonale, hematocrit >55% and congestive heart failure	Same as above
Specific indications	
Nocturnal hypoxemia	Appropriately adjusted O ₂ during sleep
Sleep apnea with nocturnal desaturation not corrected by CPAP or BPAP	Same as above
No hypoxemia at rest, but desaturation during exercise or sleep (PaO ₂ ≤55 mm Hg)	Appropriately adjusted O ₂ during sleep

SaO₂ = arterial oxygen saturation; CPAP = continuous positive airway pressure; BPAP = bilevel positive airway pressure. Adapted from American Thoracic Society. *Am J Respir Crit Care Med*. 1995;132:S77-S121.



and (5) the delivery device: nasal cannula, demand-flow device, reservoir cannula, or transtracheal oxygen catheter.⁷⁰ LTOT must be given for at least 15 hours/day to achieve benefit.^{51,52} LTOT is best provided by an oxygen concentrator and nasal cannula. The oxygen concentrator should be set at a flow of 2 to 4 L/min depending on blood gas assessments.

NONINVASIVE MECHANICAL VENTILATION (NIMV).

In the late 1980s noninvasive mechanical ventilation techniques such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP) was proved to be an effective treatment, in addition to conventional medical therapy, for patients with acute respiratory failure due to an exacerbation of COPD.⁷¹ Physiologic studies have shown that mechanical ventilation applied using either positive or negative intermittent pressure can improve gas exchange while reducing inspiratory effort in patients with stable hypercapnic chronic respiratory failure.^{72,73} Although the potential mechanisms underlying the improvement in gas exchange have not been elucidated, there seems to be general consensus that there are three possible mechanisms, namely: resting of respiratory muscles; resetting of the respiratory centers, and improvement of the respiratory mechanics.

There is no question that NIMV is effective in a hospital setting in treating hypercapnic chronic respiratory failure brought on by acute exacerbations. In the outpatient setting, however, the benefit is less clear. To date there are four published randomized controlled studies that evaluated the impact of chronic NIMV in stable COPD.⁷⁴⁻⁷⁷ Results from three of these studies^{74,76,77} suggest that chronic use of NIMV is not indicated for most patients with stable COPD.

Surgical Intervention

TRACHEOSTOMY. Many years ago tracheostomy was viewed as an intervention that would be useful in COPD. It was believed to be of value for several reasons,⁷⁸ including reduction of the anatomical dead space, facilitation of endotracheal aspiration and drainage, reduction of airway resistance with subsequent reduction in work of breathing, modification of forced residual volume, and inhibition of obstructive apneas if an overlap syndrome is present. However, it was abandoned because of its disadvantages: it is an invasive procedure that requires more support and adherence to a general rehabilitation program, requires home-care support, and has significant socioeconomic cost. As a result, tracheostomy is now reserved for more severe COPD patients in whom LTOT loses its benefit as a result of acute respiratory failure.⁷⁹⁻⁸²

LUNG VOLUME REDUCTION SURGERY (LVRS). Rediscovered by Cooper and associates⁸³ in the early 1990s, LVRS involves the resection of the most severely affected areas of lung in cases of diffuse emphysema. Clinical improvement includes relief from dyspnea, less oxygen use, increased exercise tolerance, improved lung mechanics, and improvement in overall quality of life. Appropriate candidates for LVRS include those with severe emphysema refractory to medical therapy, disabling symptoms, and evidence of severe air trapping (postbronchodilator FEV₁ <40% of predicted value) (Table 7).

TABLE 7

LUNG VOLUME REDUCTION SURGERY: INCLUSION CRITERIA.

- Post-bronchodilator FEV₁ <40% of predicted
- DLCO <50% of predicted
- TLC >100% of predicted
- Paco₂ <50 mm Hg
- Age 70 or younger

Although initial reports of LVRS were highly encouraging, enthusiasm for employing the procedure in severely affected patients was tempered by the recent report from the National Emphysema Treatment Trial (NETT).⁸⁴ This randomized, multicenter clinical trial compared mortality rates and exercise capacity in 1033 patients randomized to either LVRS or medical treatment.

Although initial reports of LVRS were highly encouraging, enthusiasm for employing the procedure in severely affected patients was tempered by the recent report from the National Emphysema Treatment Trial (NETT).

In 69 high-risk patients with FEV₁ ≤20% of predicted and either a homogeneous distribution of emphysema on computed tomography or a DLCO no more than 20% of predicted, the 30-day mortality rate postsurgery was 16% (95% CI 8.2%–26.7%), compared with a rate of 0% among 70 medically treated patients (*P* <0.001). Compared with medically treated patients, LVRS patients had small improvements at 6 months in maximal workload

($P = 0.06$), distance walked in 6 minutes ($P = 0.03$), and FEV_1 ($P < 0.001$). Moreover, quality of life was comparable between groups. Given the results of this report, the use of LVRS in high-risk patients should be discouraged.

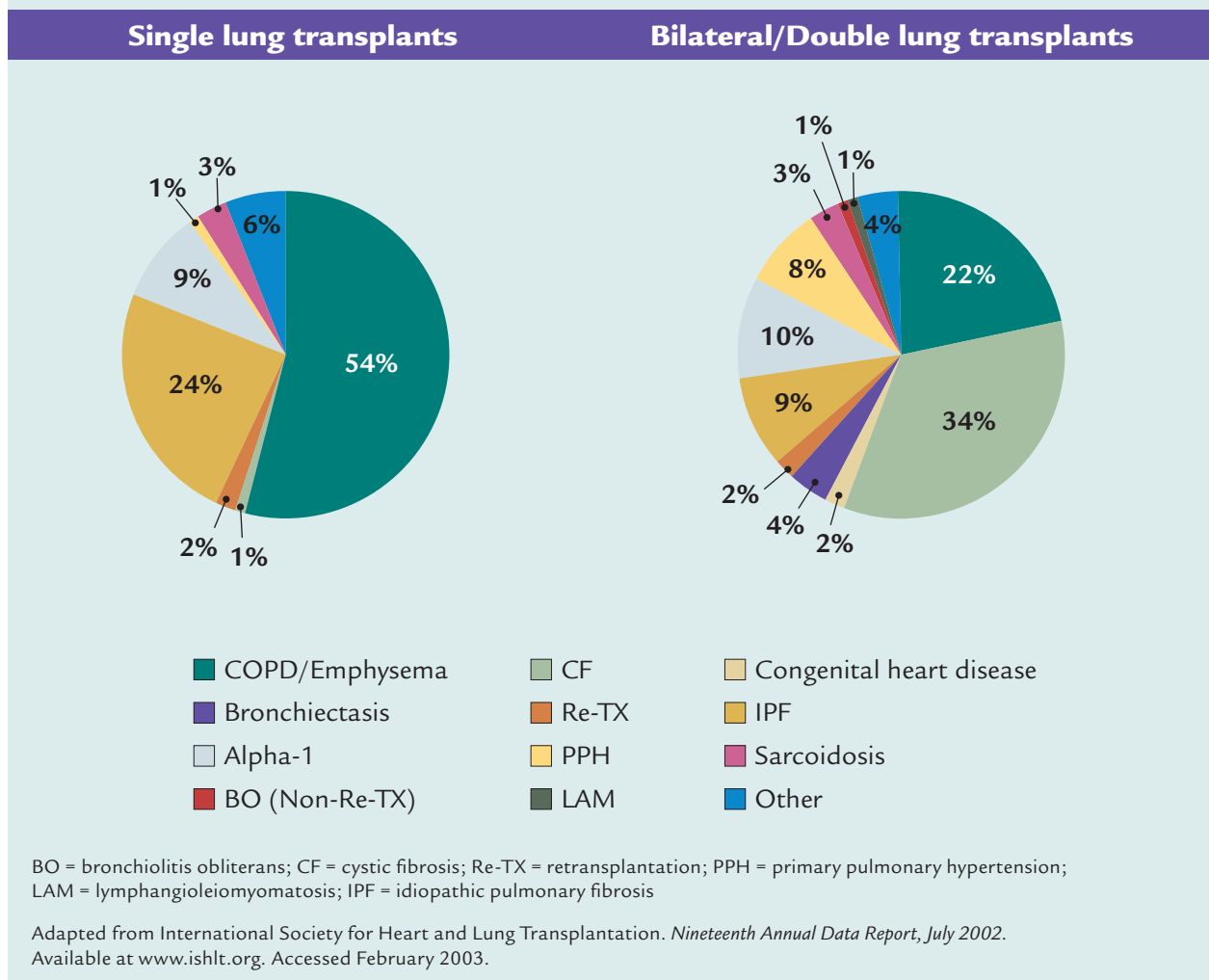
LUNG TRANSPLANTATION. According to the International Society for Heart and Lung Transplantation, COPD and α_1 -antitrypsin deficiency emphysema accounted for nearly half of all lung transplants (Figure 4).⁸⁵ In appropriately selected patients, lung transplantation can prolong life, improve functional status, and enhance

quality of life. Criteria for referral for lung transplantation include $FEV_1 < 35\%$ predicted, $Pao_2 < 55\text{--}60$ mm Hg, $Paco_2 > 50$ mm Hg, and secondary pulmonary hypertension.^{86,87}

Lung transplantation is limited by the shortage of donor organs, which has led some centers to adopt single lung transplantation (SLT). Both SLT and bilateral lung transplantation (BLT) have yielded good results. Survival rates have been similar after either procedure at 1, 2, and 3 years post-transplant,⁸⁸ but survival is higher after BLT at 5 years.

FIGURE 4

Indications for lung transplants: 1995–2001.





The common complications seen in COPD patients after lung transplantation, apart from operative mortality, are acute rejection and bronchiolitis obliterans, CMV, other opportunistic fungal (*Candida*, *Aspergillus*, *Cryptococcus*, *Pneumocystis carinii*) or bacterial (*Pseudomonas*, *Staphylococcus* species) infections, lymphoproliferative disease, and lymphomas.⁸⁸

Another limitation of lung transplantation is its cost. Hospitalization costs associated with lung transplantation have ranged from \$110,000 to well over \$200,000 (US). Costs remain elevated for months to years after surgery due to the high cost of complications and the immunosuppressive regimens⁸⁹⁻⁹³ that must be initiated during or immediately after surgery.



CONCLUSION: NONPHARMACOLOGIC INTERVENTIONS ENHANCE MEDICAL OUTCOMES

A number of exciting changes have taken place over the last 30 years in the nonpharmacologic treatment of COPD. Although none of these so far have demonstrated the impact on survival that oxygen had (albeit modest) when introduced, there are more options that can be employed for the optimal care of the COPD patient.

NEW STRATEGIES TO REDUCE COPD MORBIDITY AND MORTALITY

Taming the Epidemic: A New Treatment Paradigm

The current discussion takes COPD management efforts into the 21st century by reviewing recent and ongoing studies, diverse in design and demography, in order to approach some consensus on treatment modalities.

The anti-inflammatory properties of inhaled corticosteroids (ICS) have been credited for reducing airway hyperresponsiveness, decreasing frequency of exacerbations, and slowing the rate of decline in COPD patients' quality of life⁹⁴; yet their use for the chronic management of COPD only now is entering the mainstream.

Observational Trials Versus Randomized Controlled Trials (RCTs)

Several observational trials have compared the use of ICS alone or ICS with long-acting beta₂-agonists (LABAs) versus the use of other bronchodilators in search of a new treatment paradigm.

The use of observational studies versus randomized controlled trials (RCTs) is unsettled, as their "real-life" aspect is generally considered less rigorous than the standards of RCTs.⁹⁴ Despite their limitations, emerging evidence nonetheless suggests that the findings of observational studies for pharmacologic interventions are usually similar to those of large RCTs.⁹⁵

The choice of a reference group is critical in observational studies. For example, according to British Thoracic Society guidelines,⁹⁶ it is reasonable and responsible to compare individuals from the same database who are being cared for in a manner similar to the group given test medications, who are of similar age and with similar COPD severity. Observational studies allow researchers to evaluate a much larger group of patients than are generally seen in an RCT, with the clear

benefit of assessing large-scale morbidity and mortality and their consequences in health-care dollars spent.

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Randomized Controlled Trial Results

ISOLDE

ISOLDE, or Inhaled Steroids in Obstructive Lung Disease in Europe, was a traditional double-blind, placebo-controlled, multicenter RCT conducted in the United Kingdom in 751 patients with moderate to severe COPD.⁹⁷ The primary endpoint of ISOLDE was to measure the extent to which FEV₁ was maintained or improved with fluticasone propionate; overall health status and the frequency of exacerbations and respiratory failure events were also monitored.

FLUTICASONE REDUCED EXACERBATIONS.

Fluticasone propionate 500 mcg given twice daily significantly reduced exacerbations (by 25%, $P = 0.026$) and the rate of decline in health status, versus placebo (2.0 vs 3.2 units, $P = 0.0043$). In addition, more patients in the placebo group withdrew because of respiratory disease not associated with malignancy (25% vs 19%, $P = 0.0034$).⁹⁷

IMPROVEMENTS IN FEV₁. FEV₁ in the group receiving fluticasone was higher than in the placebo group by at least 70 mL at each time point ($P \leq 0.001$ by analysis of covariance).

Interestingly, there was no effect on the annual decline in FEV₁, but it is now acknowledged that FEV₁ by itself has relatively weak predictive powers for the incidence of COPD morbidity and mortality.⁹⁸ In fact, overall assessment of health status and exacerbations are better predictors of COPD hospital admissions and mortality than FEV₁.^{98,99}

SURVIVAL BENEFIT. ISOLDE was not a survival study, but survival trends were nonetheless observed. After researching all causes of death obtained from the UK central registry, the ISOLDE researchers found that there appeared to be a survival benefit in the fluticasone group ($P = 0.069$) over patients taking placebo during the 3 years of follow-up. So, based on an analysis of recaptured data, results showed that patients taking fluticasone lived longer.⁹⁷

The ISOLDE investigators concluded that, in patients with moderate to severe COPD, administration of fluticasone resulted in fewer exacerbations, a reduced rate of decline in health status, and higher FEV₁ values versus placebo.⁹⁷

Observational Studies

Studies of Repeat Hospitalization and Mortality

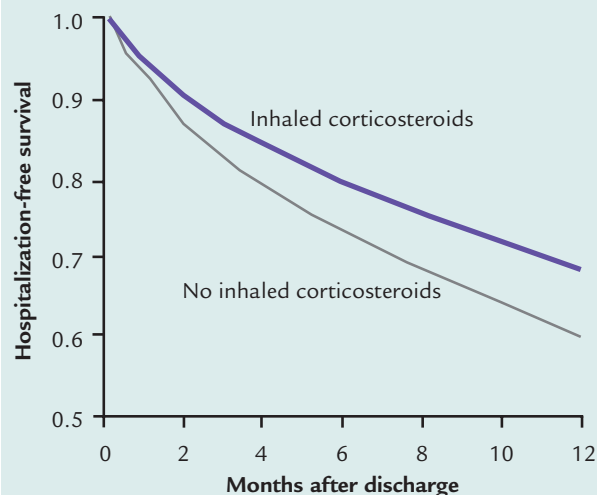
CANADIAN STUDY. In a Canadian study conducted according to a longitudinal cohort design, Sin and Tu examined the association between ICS use and the rate of repeat hospitalization and mortality in elderly (65 and older) patients recently hospitalized for COPD.⁹⁴

The investigators searched the Ontario segment of the Canadian Institute for Health Information hospital discharge database to identify all elderly patients discharged with an ICD-9-CM diagnosis¹⁰⁰ of COPD between April 1, 1992 and March 31, 1997. They further limited the population to those individuals who received prescriptions within 90 days postdischarge for ICS (beclomethasone, budesonide, triamcinolone, or fluticasone) or other airways medications (inhaled beta₂-agonists, anticholinergics, oral corticosteroids, or theophylline derivatives) and/or antibiotics; 22,620 patients fit this description. COPD patients were monitored through (1) their first repeat hospitalization for COPD, (2) time of death, (3) 365 days after discharge from the index admission, or (4) at the end of the study (March 31, 1998), whichever was earliest. These time limits ensured that all patients in the cohort had a potential for 1 year of observation.⁹⁴

REDUCED RISK WITH ICS. Figure 5 shows the adjusted probability of hospitalization-free survival in patients who did or did not receive ICS within 90 days of hospital discharge. Sin and Tu found that patients who received ICS had a combined 26% lower adjusted relative risk (RR 0.74, 95% CI 0.71–0.78) for repeat hospitalization or death than were those who did not receive ICS. The relative risk reduction in all-cause mortality was 29% (95% CI 0.22–0.35) and for repeat hospitalization, 24% (95% CI 0.20–0.29) in favor of patients given ICS (Table 8).

FIGURE 5

Adjusted probability of hospitalization-free survival: Sin & Tu observational study.



Sin DD, Tu JV. *Am J Respir Crit Care Med.* 2001;164:580-584.

TABLE 8

INHALED CORTICOSTEROIDS: EFFECT ON RELATIVE RISK FOR COPD PATIENTS POSTDISCHARGE.

	Mortality relative risk	Readmission relative risk
Inhaled corticosteroids	0.71	0.76
Beta ₂ -adrenergics	1.00	1.00
Ipratropium bromide	1.00	1.02
Oral theophylline	1.01	1.20
Antimicrobials	1.08	1.17
Oral corticosteroids	0.37	2.09

Sin DD, Tu JV. *Am J Respir Crit Care Med.* 2001;164:580-584.

After adjusting their analysis by means of the Charlson comorbidity score,¹⁰¹ a validated instrument for measuring comorbidity, Sin and Tu found that neither age nor comorbidity materially affected the relationship between ICS use and either mortality or repeat hospitalization. The investigators concluded that ICS therapy reduced hospitalizations and extended survival in elderly patients with COPD.⁹⁴

...ICS therapy reduced hospitalizations and extended survival in elderly patients with COPD.

These data support ICS use in older patients with prior COPD hospitalization and corroborate those of Paggiaro and associates.¹⁰² These authors conducted an RCT in older (age 50 to 75) COPD patients that showed an important beneficial effect of ICS on patient outcomes.¹⁰² In a multicenter trial conducted in 281 outpatient current or ex-smokers enrolled from 15 countries, investigators found that patients' age, sex, baseline FEV₁, bronchodilator reversibility, or smoking habit did not influence response to therapy, and that significantly fewer patients given fluticasone had moderate or severe exacerbations than those given placebo (60% vs 86%, $P < 0.001$).¹⁰²

REPLICATING CANADIAN STUDY OVERSEAS. The United Kingdom General Practice Research Database (GPRD) is the largest worldwide population-based sample used for conducting outcomes research. It includes patient records from 5% of all UK primary care practices since 1987 in a continuous longitudinal database encompassing more than 3 million patients and 50 million patient-years. The GPRD has advantages over health maintenance organization (HMO) databases in the United States, in which elderly people are frequently lost to follow-up, and pharmaco-epidemiological databases in Canada, because until recently combined use of ICS and LABAs is not commonly seen among Canadian COPD patients.

One GPRD study¹⁰³ sought to reproduce the hypothesis of the Sin and Tu study. The premise that COPD patients treated with ICS, alone or in combination with LABAs, could avoid repeat hospitalization and demonstrate increased survival compared to patients treated without ICS or LABAs was again being tested, this time by Soriano and associates in a COPD population in the United Kingdom. A total population of 4263 was enrolled, of whom 3636 received at least one prescription for ICS or LABAs in the first 90 days after hospital discharge. Specifically, 3049 patients received prescriptions for ICS

only, 91 took LABAs only; 496 patients received both ICS and LABAs, and 627 patients received reference medication, generally short-acting bronchodilators, but not ICS or LABAs.

After 1 year, rehospitalization occurred in 13.2% of the reference COPD patients, in 14.0% of users of LABAs only, 12.3% of users of ICS only, and in 10.4% of users of ICS and LABAs. In the same respective groups, mortality occurred in 24.3% of the patients who received neither ICS nor LABAs, compared with 17.3% of the LABA-only group (hazard ratio [risk of mortality] 0.62), 17.7% of the ICS-only group (HR 0.79), and 10.5% of patients who received both ICS and LABAs (HR 0.48). The authors concluded that in this UK population of COPD patients, regular use of ICS, whether alone or in combination with LABAs, was associated with increased survival and fewer rehospitalizations relative to patients treated without ICS or LABAs. These are notable findings, since survival rates of ICS-only users and those who used both ICS and LABAs are statistically significant ($P < 0.04$ and $P < 0.001$, respectively).¹⁰³

...Survival rates of ICS-only users and those who used both ICS and LABAs are statistically significant...[relative to those treated without ICS or LABAs]

SAME POPULATION, ANOTHER ANALYSIS. In another study, Soriano and associates⁹⁵ also compared all-cause mortality over a 3-year period in 1045 COPD patients with regular prescriptions of fluticasone and/or salmeterol to that in 3620 COPD reference patients with regular prescriptions of bronchodilators but not inhaled corticosteroids or LABAs.

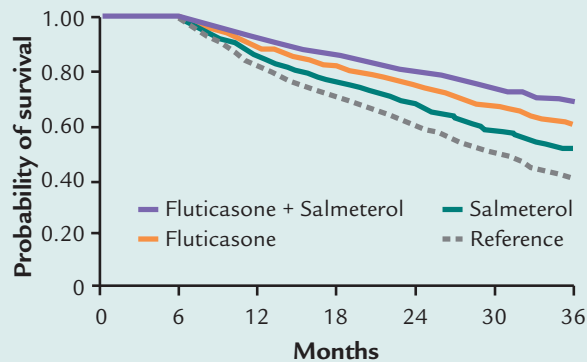
Users of fluticasone or salmeterol were stratified into three treatment groups: users of salmeterol alone ($N = 297$), users of fluticasone alone ($N = 431$), and combined users of both fluticasone and salmeterol ($N = 317$). Initiation of pharmacotherapy was taken as the first date of regular use (first prescription). Initiation of pharmacotherapy for the combined fluticasone and salmeterol group was taken as the first date of overlap of both drugs (the start date of the second regular drug). Patients on regular treatment with ICS or LABAs other than fluticasone and salmeterol after COPD diagnosis were excluded.

COPD patients who were regular users of fluticasone and/or salmeterol showed significantly greater crude 3-year survival rates than those patients in the reference



FIGURE 6

Adjusted survival rates comparing fluticasone and salmeterol (alone and in combination) vs. inhaled bronchodilators.



Soriano JB, et al. *Eur Respir J.* 2002;20:819-826.

group (78.6% vs. 63.6%; Kaplan-Meier $P < .05$). In addition, significant differences in survival were observed in COPD patients using fluticasone and salmeterol ($P = .0008$) and fluticasone alone ($P = .0028$) as compared to the reference group (Figure 6).⁹⁵

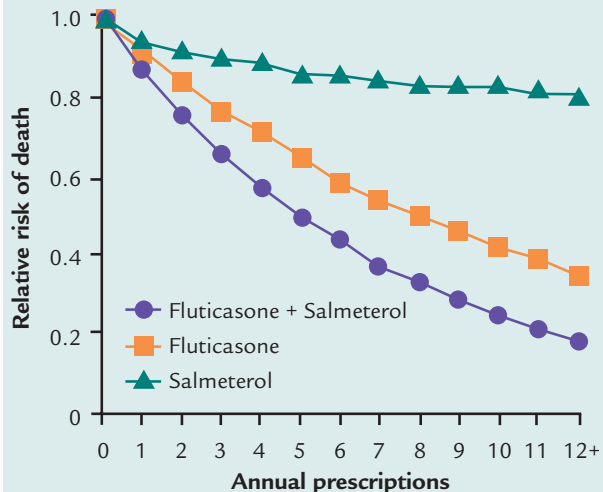
In addition, mortality decreased with increased administration (number of prescriptions) of fluticasone and salmeterol (Figure 7).⁹⁵ Rate ratios declined by 13% as a result of an additional annual combined prescription (relative risk 0.87 [95% CI, 0.80-0.95]) and the rate among combined FP and salmeterol users receiving five or more prescriptions of both drugs was reduced by >50% versus the reference group.

US OBSERVATIONS. Buoyed by the findings of the Canadian and UK GPRD observational studies, Mapel and colleagues¹⁰⁴ examined the relationship between survival and use of ICS and/or LABAs in a retrospective observational study conducted in the United States.

The study was conducted in two managed-care populations: Lovelace Health Plan, a group and network model HMO in New Mexico with approximately 240,000 members in 2001, and Kaiser-Permanente Georgia Health Plan, a group and network model HMO in Atlanta with approximately 280,000 members in 2001. Study patients were plan members during 1995-2000, age ≥ 40 years, with at least two outpatient claims or one hospital admission for COPD. 'Exposed' COPD patients ($N = 1288$)

FIGURE 7

Inhaled corticosteroids and long-acting beta₂-agonists: Decreased mortality with increased number of prescriptions.



Soriano JB, et al. *Eur Respir J.* 2002;20:819-826.

had ≥ 90 days use of ICS, LABAs, or concurrent ICS plus LABAs. 'Comparison' COPD patients ($N = 397$) had no use of ICS or LABAs but ≥ 90 days exposure to another respiratory drug. Patients with cystic fibrosis, bronchiectasis, or lung cancer were excluded.

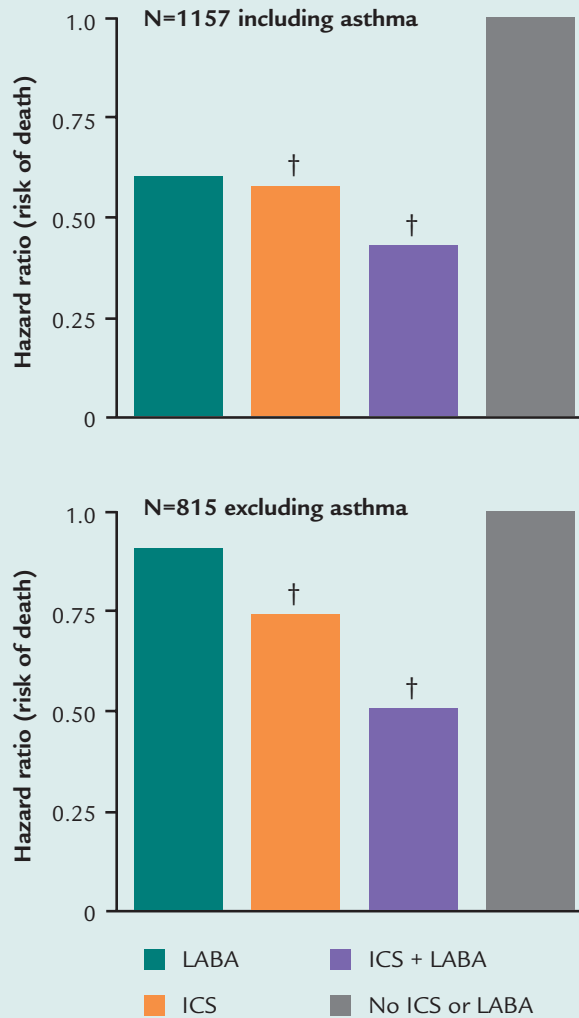
Patients who met the eligibility criteria were stratified into one of four treatment groups: Those exposed to ICS alone ($N = 786$), patients exposed to LABAs alone ($N = 170$), and those exposed to ICS plus LABAs ($N = 332$).

In a Cox proportional hazards model that controlled for age, sex, comorbidities, COPD severity, and asthma diagnosis and severity ($N = 1157$), a reduced risk for death was found for ICS exposure (HR 0.58, $P < 0.0001$) and ICS plus LABA exposure (HR 0.43, $P < 0.0001$).¹⁰⁴

Because this was an observational study, the authors anticipated that a concomitant asthma diagnosis might introduce a selection bias or misclassification error associated with an improved outcome, since ICS and LABA are also used to treat asthma. Therefore, a second proportional hazards model that included only those COPD patients with no diagnosis of asthma ($N = 815$) was developed. This analysis also yielded reduced risk with ICS (HR 0.74, $P < 0.05$) and ICS plus LABA (HR 0.51) (Figure 8).¹⁰⁴

FIGURE 8

Relative risk of death* in COPD patients including or excluding those with a history of asthma.



* Cox proportional hazards model controlling for age, gender, health plan, number of COPD outpatient visits, number of hospitalizations, and Charlson index.

† Statistically significant.

Mapel DW, et al. *Chest*. 2002;122(suppl):74S.

Why Do ICS Effect Survival?

Because ICS have not modified the long-term decline in FEV₁ in clinical trials,^{97,105-107} the GOLD Guidelines recommend their continued use in instances where a patient demonstrates improvement in FEV₁ with their use or has severe obstruction with frequent exacerbations (Table 9). Although inflammation is acknowledged in the guidelines, the emphasis is on airflow obstruction.¹⁰⁸ Thus, clinicians may erroneously assume that if a treatment does not improve FEV₁, it does not benefit the patient.

TABLE 9

GOLD GUIDELINES FOR TREATING COPD BASED ON SEVERITY.

Stage	Treatment
0: At Risk	Avoid risk factors Smoking cessation
I: Mild	Avoid risk factors Short-acting bronchodilator PRN
IIA: Moderate	Avoid risk factors Regular therapy with ≥1 bronchodilators Inhaled corticosteroids if significant symptoms and lung function response Rehabilitation
IIB: Moderate	Avoid risk factors Regular therapy with ≥1 bronchodilators Inhaled corticosteroids if significant symptoms and lung function response or if repeated exacerbations Rehabilitation
III: Severe	Avoid risk factors Regular therapy with ≥1 bronchodilators Inhaled corticosteroids if significant symptoms and lung function response or repeated exacerbations Rehabilitation Treatment of complications Long-term O ₂ therapy for hypoxic respiratory failure Evaluate for surgical treatment

Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. NHLBI/WHO Workshop Report; March 2001. Available at www.goldcopd.com/workshop.html. Accessed February 2003.



The Impact of COPD Exacerbations

The most likely means by which ICS could impact survival is through reduction in the number and severity of COPD exacerbations.^{97,102,109,110} Compared with stable COPD, acute exacerbation of COPD is associated with increased short-term mortality. The mortality rate in patients requiring intensive care unit (ICU) treatment for respiratory failure has been described as 11% to 24% in the hospital, and 43% to 59% over 1 year.¹¹¹

Compared with stable COPD, acute exacerbation of COPD is associated with increased short-term mortality.

In patients who survive exacerbations of COPD, there is evidence of substantial reductions in functional status and quality of life. Functional status following exacerbation is substantially worse than pre-exacerbation values in as many as one third of patients; in many cases, patients may remain incapacitated for several months.^{112,113} In one study, quality of life was worse in patients with frequent exacerbations than in those with less frequent exacerbations, even though symptoms and physiological parameters were similar.¹¹⁴ Low quality of life is a predictor of death in COPD.¹¹⁵

Readmission following hospitalization for acute exacerbation of COPD is frequent. In one study, nearly half of discharged patients were readmitted an average of nearly two times in the 6 months after discharge.¹¹⁶ In several studies,^{117,118} patients with exacerbations of underlying COPD accounted for 15% to 25% of ED visits for dyspnea.

EXACERBATIONS AND INFLAMMATION. There is little known about how the pattern of airway inflammation associated with COPD—characterized by increased numbers of CD8+ T lymphocytes, mononuclear cells, neutrophils, and macrophages—is related to exacerbations. However, a recent randomized placebo-controlled study of COPD patients¹¹⁰ revealed that inhaled fluticasone significantly reduced the number of subepithelial mast cells and the CD8:CD4 ratio in the epithelium, and the CD4+ cells were significantly raised in the placebo group in both the subepithelium and epithelium. These findings correlate with the findings of Burge and associates.⁹⁷

Although knowledge about the mechanisms of COPD pathogenesis and acute exacerbations is far from complete, it is believed that ICS may suppress components of the inflammatory response that increase susceptibility to exacerbations, and may also reduce the risk for complications when exacerbations do occur.¹⁰⁴



CONCLUSION: CURRENT MEDICAL THERAPY CAN SIGNIFICANTLY IMPACT QUALITY OF LIFE AND MORTALITY

Recent COPD studies that have observed positive clinical effects of treatment with ICS and LABAs suggest that it is time to reconsider primary outcomes measures for clinical studies of COPD. The outcomes of most importance to COPD patients are relief of symptoms, reduction in the frequency and severity of exacerbations, improvement in quality of life, and prolonged survival. The results of these studies indicate that ICS, given alone or in concert with LABAs, have a positive impact on these factors. Current assumptions underlying current COPD treatment warrant re-examination, with a view toward adopting a more comprehensive approach toward meeting these desired goals of COPD patients.

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Post-Test Questions (fax answer sheet on following page)

1. The GOLD Guidelines: which statement is false?

- a. Symptoms serve as the primary basis for defining severity
- b. Severity is based on spirometric measurement
- c. Severity is classified into one of four stages
- d. A step-care approach for therapy is employed

2. The estimated combined direct and indirect costs of COPD in the United States are said to be:

- a. \$ 850 million
- b. \$ 4 billion
- c. \$14 billion
- d. \$23 billion

3. Depression is believed to occur in ___ % of COPD outpatients:

- a. 7%
- b. 12%
- c. 21%
- d. 37%

4. Which statement is true?

- a. Most COPD patients are normoxemic during rest
- b. Many patients in Stage IIA COPD develop respiratory failure during sleep
- c. The most severe episodes of nocturnal hypoxemia occur during REM sleep
- d. There is little correlation between chronic bronchitis and obstructive sleep apnea syndrome

5. Which statement is false?

- a. Nutritional support must take into account the body mass index of the patient and the degree of involuntary weight loss
- b. Nutritional support is indicated in COPD patients whose BMI is $<18 \text{ kg/m}^2$
- c. Nutritional support is indicated in COPD patients with BMIs of $<25 \text{ kg/m}^2$ in the event of involuntary weight loss
- d. Nutritional support emphasizing fats rather than carbohydrates may increase caloric intake and ventilatory workload

6. The optimal exercise program for COPD patients includes:

- a. Breathing exercises
- b. Training with free weights
- c. Walking and arm motion exercises
- d. Scuba diving

7. Long-term oxygen therapy is prescribed based on:

- a. Evidence of hypoxemia
- b. Evidence of cor pulmonale
- c. Degree of dyspnea
- d. Degree of airflow obstruction

8. Which clinical factor is not considered part of the indicators for lung volume reduction surgery?

- a. Postbronchodilator $\text{FEV}_1 < 40\%$ of predicted
- b. $\text{PaCO}_2 < 50 \text{ mm Hg}$
- c. $\text{PaO}_2 < 50 \text{ mm Hg}$
- d. Age 70 or younger

9. Which statement regarding exacerbations of COPD is considered false?

- a. Exacerbations of COPD have little impact on short-term mortality
- b. Exacerbations of COPD can result in substantial reductions of functional status
- c. Exacerbations of COPD have an adverse impact on health-related quality of life
- d. Readmission occurs in nearly 50% of patients requiring hospitalization for exacerbation of COPD

10. Readmission following hospitalization for exacerbations of COPD: Which statement is true?

- a. Inhaled corticosteroids have been shown to reduce hospital readmissions in large retrospective studies
- b. Inhaled corticosteroids have been shown to consistently improve FEV_1 following exacerbations of COPD
- c. Inhaled corticosteroids are of little value in advanced COPD
- d. Inhaled corticosteroids are contraindicated in COPD patients who experience frequent exacerbations



COPD MORTALITY: THAT WAS *THEN* – THIS IS *NOW!*

After completing the CME Post-Test Answer Form, Participant Identification, and the Program Evaluation, **fax to 1-800-267-0135 or 1-847-579-1472.** You can also complete this information online at:

<http://www.chestnet-cme.org/copd.htm>

Please allow six to eight weeks for grading of the test and receipt of your CME certificate.

CME POST-TEST ANSWER FORM *(Shade in the correct circle)*

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| 1. <input type="radio"/> a | <input type="radio"/> b | <input type="radio"/> c | <input type="radio"/> d | 6. <input type="radio"/> a | <input type="radio"/> b | <input type="radio"/> c | <input type="radio"/> d |
| 2. <input type="radio"/> a | <input type="radio"/> b | <input type="radio"/> c | <input type="radio"/> d | 7. <input type="radio"/> a | <input type="radio"/> b | <input type="radio"/> c | <input type="radio"/> d |
| 3. <input type="radio"/> a | <input type="radio"/> b | <input type="radio"/> c | <input type="radio"/> d | 8. <input type="radio"/> a | <input type="radio"/> b | <input type="radio"/> c | <input type="radio"/> d |
| 4. <input type="radio"/> a | <input type="radio"/> b | <input type="radio"/> c | <input type="radio"/> d | 9. <input type="radio"/> a | <input type="radio"/> b | <input type="radio"/> c | <input type="radio"/> d |
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PARTICIPANT IDENTIFICATION *(Please print clearly)*

Name: _____
First Last Middle Initial

Trail: _____ *(MD, DO, NP, PA, RN, other)* Degree: _____

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Please complete program evaluation on back of this page →

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Program Evaluation

Your evaluation of this program is essential to us in planning future CME programs.

Please answer the following questions:

1. Accuracy and timeliness of content.

Excellent Satisfactory Poor

2. Relevance to your daily practice.

Excellent Satisfactory Poor

3. Impact on your professional effectiveness.

Excellent Satisfactory Poor

4. Freedom from commercial bias.

Excellent Satisfactory Poor

5. Relevance of the content to the learning objectives.

Excellent Satisfactory Poor

6. Effectiveness of the teaching/learning objectives.

Excellent Satisfactory Poor

7. Learning Objectives: Now that you read this monograph, are you able to:

a. Appraise the driving forces behind the current and future burdens of COPD in the US?

Yes No

b. Illustrate effective uses of nonpharmacologic interventions in various COPD patients?

Yes No

c. Examine current literature on many COPD treatment regimens?

Yes No

d. Contrast available COPD therapy outcomes with that of the recent past?

Yes No

8. How will you use what you have learned from this activity in patient care?

9. What other questions on this topic do you still have?

Cut along dashed line



