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Executive Summary

Canadian Thoracic Society Recommendations for Management of Chronic Obstructive Pulmonary Disease – 2003

Résumé

Recommandations de la Société Canadienne de Thoracologie relativement au traitement de la Maladie Pulmonaire Obstructive Chronique – 2003

(Revised translation/traduction révisé)

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Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2003

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Chronic obstructive pulmonary disease (COPD) is a common cause of disability and death in Canada. Moreover, morbidity and mortality from COPD continue to rise and the economic burden is enormous. The main goal of the Canadian Thoracic Society (CTS) Evidence-Based Guidelines is to optimize early diagnosis, prevention and management of COPD in Canada. Targeted spirometry is strongly recommended to expedite early diagnosis in smokers and exsmokers who develop respiratory symptoms, and who are at risk for COPD. Smoking cessation remains the single most effective intervention to reduce the risk of COPD and to slow its progression. Education, especially self-management plans, are key interventions in COPD. Therapy should be escalated in accordance with the increasing severity of symptoms and disability. Long acting anticholinergics and beta$_2$-agonist inhalers should be prescribed for patients who remain symptomatic despite short-acting bronchodilator therapy. Inhaled steroids should not be used as first line therapy in COPD, but have a role in preventing exacerbations in patients with more advanced disease who suffer recurrent exacerbations. Management strategies consisting of combined modern pharmacotherapy and nonpharmacotherapeutic interventions (eg, pulmonary rehabilitation/exercise training) can effectively improve symptoms, activity levels, and quality of life, even in patients with severe COPD. Acute exacerbations of COPD cause significant morbidity and mortality and should be treated promptly with bronchodilators and a short course of oral steroids; antibiotics should be prescribed for purulent exacerbations. Patients with advanced COPD and respiratory failure require a comprehensive management plan that incorporates structured end-of-life care.

Key Words: *Chronic obstructive pulmonary disease; Management; National guidelines*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of disability and death in Canada and throughout the world. The main goals of this educational initiative of the Canadian Thoracic Society (CTS) are to optimize the prevention and management of COPD in Canada; to increase awareness of this common condition; and to identify areas for future scientific research. The guidelines are primarily intended to meet the needs of family physicians. However, all health professionals involved in the care of patients with COPD should find this document useful. This document highlights the importance of a comprehensive management plan for patients with more advanced symptomatic disease. A key message that emerges is that combined modern pharmacotherapy and non-pharmacotherapeutic interventions effectively improve symptoms, activity levels and quality of life, even in patients with severe COPD.

The COPD/Rehabilitation Committee of the CTS was invited to develop a document that outlined the current optimal management of COPD in Canada.

The objectives of the committee were as follows:

1. To develop practice recommendations for the management of COPD that were based on evidence arising from a critical review of the scientific literature;
2. To develop best practice recommendations based on consensus where evidence from randomized clinical trials was not available. Consensus decisions were based on a thorough review of the available literature and followed broad consultation with experts in the care of COPD patients; and
3. To enhance the future management of COPD by identifying areas that should be targeted for urgent research.

The strength of the scientific evidence supporting each recommendation was quantified using a schema previously used by the CTS for guidelines development (Table 1) (1). The development process is summarized in Table 2.

TABLE 1
Levels of evidence

Level
1. Evidence from one or more randomized trials
2. Evidence from one or more well-designed cohort or case-control study
3. Consensus from expert groups based on clinical experience
Evidence was further subdivided into a number of categories
A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation for or against use
D. Moderate evidence to support a recommendation against use
E. Good evidence to support a recommendation against use

TABLE 2
Summary of the development process

CTS Review Panel selected
↓
Team leaders selected + 11 major topics (draft 1)
↓
First panel conference – topics reviewed
Committee recommendations (draft 2)
↓
Second panel conference – topics reviewed
Committee recommendations (draft 3)
↓
Preview of CTS Recommendations at Halifax National Consensus Conference
Feedback from affiliated societies/organizations, pharmaceutical sponsors and external experts
↓
Third panel conference – review of feedback, final revision
Final document submission – *CRJ* (review, summary), Internet, family physicians

CRJ Canadian Respiratory Journal*; CTS Canadian Thoracic Society*

DEFINITION

COPD is a respiratory disorder largely caused by smoking, which is characterized by progressive, partially reversible airway obstruction, systemic manifestations, and increasing frequency and severity of exacerbations.

Cardinal symptoms experienced by patients with COPD are shortness of breath and exercise intolerance. The symptoms are usually insidious in onset, typically progressive and characterized by frequent exacerbations. Although initially confined to the lungs, this chronic inflammatory process, which is the pathological basis for COPD, is accompanied by systemic manifestations. Skeletal muscle dysfunction (2), right heart failure (3), secondary polycythemia (4), altered nutritional status (5) and depression (6) complicate more advanced disease. Impairment in respiratory function and systemic manifestations together contribute to significant disability and handicap, causing reduced health-related quality of life.

Objective demonstration of air flow obstruction by spirometry is mandatory for the diagnosis of COPD. COPD is usually suspected in patients with a significant smoking history who present with progressive exertional dyspnea, cough and sputum production. All patients with suspected COPD should have their lung function assessed by spirometry. The forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio is the most important measurement for distinguishing an obstructive impairment (7). A post bronchodilator FEV_1 of less than 80% of the predicted value in association with an FEV_1/FVC ratio of less than 0.7 defines air flow obstruction, and both are necessary to establish a diagnosis of COPD.

EPIDEMIOLOGY OF COPD IN CANADA

Mortality

In 1999, COPD was the fourth leading cause of death in men and the fifth in women in Canada (8). In that year, 5544 men and 3974 women died of COPD. Mortality rates in women increased by 53% from 1988 to 1999 and are still increasing (Figure 1). The rate among men decreased by 7% within this time frame. Mortality rates increase rapidly over 75 years of age. The change in age structure of the population with an increasing number of people aged over 65 years will result in

continued increases in mortality rates for COPD (particularly in women) in the foreseeable future. Furthermore, the estimated mortality rate is a significant underestimation (9).

Prevalence

According to the 2000/2001 Canadian Community Health Survey (CCHS), 3.9% of Canadians aged 35 years or more (466,812 adults) have probable COPD based on self-reporting of diagnoses made by health professionals (8). The Panel agreed that these figures likely underestimate the true prevalence of COPD because a diagnosis is often not made until the patient has advanced disease. Studies have estimated that more than 50% of patients with COPD remain undiagnosed in the community (10).

Health care services in Canada

In Canada in 2000/2001, COPD was the seventh most common cause of hospitalization for men and the eighth for women. Hospitalizations were greater for patients over 65 years of age. Risk of rehospitalization is high (approximately 40%) among patients with COPD (8).

Health costs

The economic burden for COPD in Canada is enormous. A Health Canada document published in 1998 reported that CDN$467 million were spent on hospital care and drugs for COPD, and direct costs (premature mortality, long and short term disability) were estimated at CDN$1.2 billion, with total costs, therefore, estimated at CDN$1.67 billion. This figure significantly underestimates the true costs because it does not include physician costs or costs related to community-based health services (8). The full report is available on the Web site <www.hc-sc.gc.ca/pphb-dgspsp/publicat/ebic-femc98>.

PATHOPHYSIOLOGY OF COPD

COPD is characterized by complex and diverse pathophysiological manifestations. Persistent inflammation of the small and large airways, and the lung parenchyma and its vasculature occurs in a highly variable combination that differs from patient to patient (Figure 2). In Canada, cigarette smoke is the main inflammatory trigger in COPD. Our understanding of this inflammatory process continues to grow (11-17). Macrophages, T lymphocytes (predominately CD8+) and neutrophils are found in increased numbers throughout the lungs. These activated inflammatory cells release a variety of mediators including leukotriene B4, interleukin-8, tumor necrosis factor alpha, and others capable of damaging lung structure and sustaining ongoing neutrophilic inflammation (18-24). The inflammatory process in COPD persists long after the inciting stimulus (cigarette smoke) is withdrawn (17). It is clear that the inflammatory process in COPD is different in many important respects from that in asthma.

Expiratory flow limitation is the pathophysiological hallmark of COPD. This arises because of intrinsic airway factors that increase resistance (ie, mucosal inflammation and/or edema, airway remodelling and secretions) and extrinsic airway factors (ie, reduced airway tethering from emphysema and regional extraluminal compression by adjacent overinflated alveolar units) (Figure 2) (21,22). Emphysematous destruction

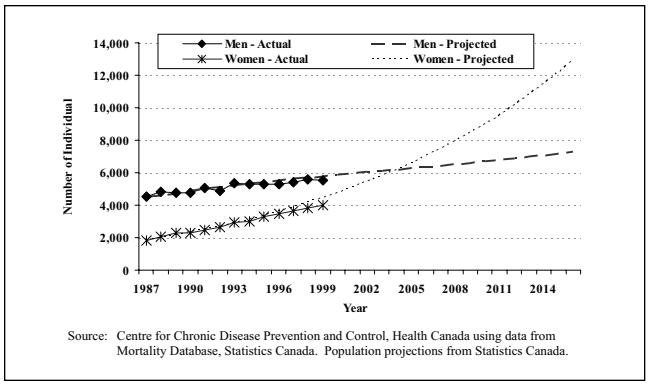

Figure 1) *Number of chronic obstructive pulmonary disease deaths, actual and projected, in Canada between 1987 and 2016*

also reduces elastic lung recoil and, thus, the driving pressure for expiratory flow, further compounding flow limitation. Further modulation of airway calibre in COPD is provided by the autonomic nervous system, which can be pharmacologically manipulated. Thus, cholinergic and sympathetic efferent activity influence airway resistance and the extent of flow limitation.

These pathophysiological changes in the airways and lungs ultimately give rise to the clinical manifestations of COPD – recurrent, persistent cough; propensity for exacerbations; and progressive shortness of breath. Expiratory flow limitation with dynamic collapse of the small airways compromises the ability of patients to expel air during forced and quiet expiration; thus, air trapping and lung overinflation occurs. The volume of air in the lungs at the end of quiet expiration (ie, end expiratory lung volume) is increased and is a continuous dynamic variable in COPD. When the breathing rate acutely increases (and expiratory time diminishes), as, for example, during exercise in COPD, there is further dynamic lung overinflation as a result of air trapping, which has serious mechanical and sensory consequences (25). Over many years, the respiratory system adjusts to lung overinflation: the rib cage reconfigures to accommodate large lung volumes and there is temporal adaptation of the ventilatory muscles (particularly the diaphragm) to maintain adequate pressure-generating capacity despite the mechanical disadvantage. However, such adaptations are quickly overwhelmed when ventilatory demand acutely increases (eg, during exercise). Acute-on-chronic hyperinflation has been shown to contribute to exertional shortness of breath, reduced ventilatory capacity and exercise limitation in COPD (25-27).

Oxygen uptake and carbon dioxide elimination by the lungs are compromised because of regional inequalities of ventilation and perfusion throughout the lungs. Wasted ventilation leads to high ventilatory demands to maintain blood gas homeostasis. Destruction of the vascular bed due to emphysema, together with the vasoconstrictor effects of chronic hypoxia, lead to pulmonary hypertension and right heart failure (24). In more advanced COPD, when patients become immobilized with dyspnea, there are measurable metabolic and structural abnormalities of peripheral locomotor muscles. This peripheral

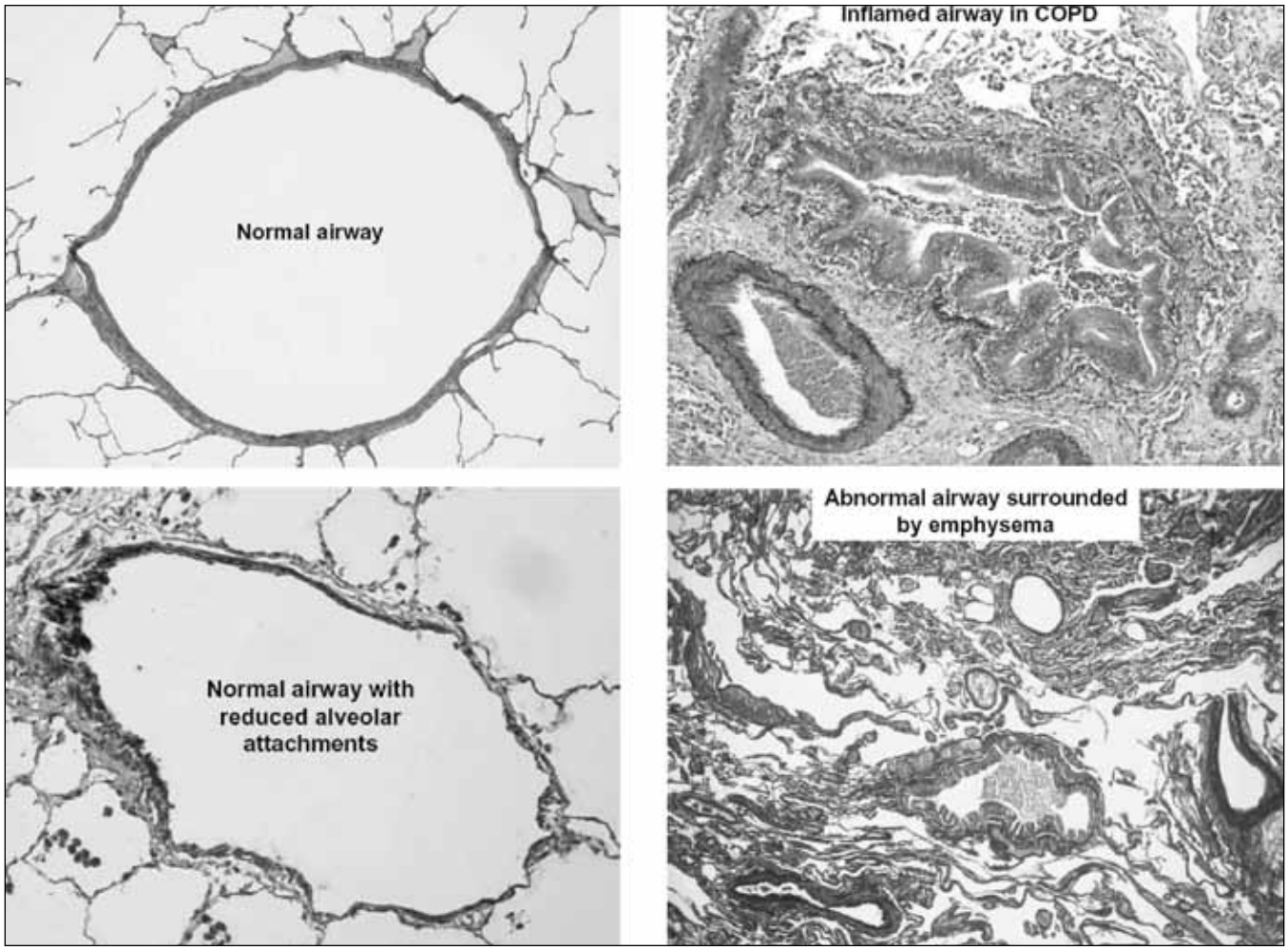

Figure 2) *Pathology of a normal airway, a normal airway with reduced alveolar attachments, an inflamed airway in chronic obstructive pulmonary disease (COPD) and an abnormal airway surrounded by emphysema. Courtesy of Dr James C Hogg, University of British Columbia, Vancouver, British Columbia*

muscle dysfunction, which contributes to exercise intolerance, results from the combined effects of immobility, altered nutritional status, prolonged hypoxia and, possibly, to sustained systemic inflammation (25).

Current management paradigms in COPD are based on our knowledge of the pathophysiology of this complex condition. Thus, pharmacological and nonpharmacological interventions are used to partially reverse or alter the fundamental pathophysiological abnormalities outlined above.

CLINICAL ASSESSMENT

The importance of early diagnosis

Mass screening for COPD among asymptomatic smokers is not supported by evidence and, therefore, is not recommended. Barriers to the early identification of COPD include poor public awareness of the condition and the development of adaptive strategies by patients to avoid breathlessness over time and delay seeking medical attention until disability has become well advanced. The Panel recommends performing targeted spirometric testing to establish early diagnosis in individuals at risk for COPD. Successful early detection requires the availability of high-quality spirometry and interpretation. Spirometric assessments can be undertaken effectively in primary care. Adequate training and regular application of good technique are essential, and many primary care physicians opt to have the assessment undertaken at a specialist centre or hospital pulmonary function testing unit (28-31). The Panel recommended the following criteria to help identify patients with possible COPD who require spirometric confirmation:

1. Smoker or exsmoker more than 40 years old;
2. Patients with persistent cough and sputum production;
3. Patients who experience frequent respiratory tract infections; and
4. Patients who report progressive activity-related shortness of breath.

Objective indexes of airway obstruction often fluctuate over time but must persist and not be fully reversible if a diagnosis of COPD is to be made. Accordingly, it is possible that the diagnosis of COPD cannot be established at the first evaluation. Regular follow-up with serial spirometry on an annual basis may be required.

TABLE 3
Canadian Thoracic Society chronic obstructive pulmonary disease (COPD) classification by symptoms/disability*

COPD stage	Symptoms
At risk (does not yet fulfill the diagnosis of COPD)	Asymptomatic smoker, exsmoker or chronic cough/sputum, but post-bronchodilator $FEV_1/FVC \geq 0.7$ and/or $FEV_1 \geq 80\%$ predicted
Mild	Shortness of breath from COPD† when hurrying on the level or walking up a slight hill (MRC 2)
Moderate	Shortness of breath from COPD† causing the patient to stop after walking about 100 m (or after a few minutes) on the level (MRC 3-4)
Severe	Shortness of breath from COPD† resulting in the patient too breathless to leave the house, breathlessness after undressing (MRC 5), or the presence of chronic respiratory failure or clinical signs of right heart failure

**Post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio less than 0.7 and FEV_1 less than 80% predicted are both required for the diagnosis of COPD to be established. †In the presence of non-COPD conditions that may cause shortness of breath (eg, cardiac dysfunction, anemia, muscle weakness, metabolic disorders), symptoms may not appropriately reflect COPD disease severity. Classification of COPD severity should be undertaken with care in patients with comorbid diseases or other possible contributors to shortness of breath. MRC Medical Research Council scale*

Evaluation of the COPD patient

History: Clinical assessment begins with a thorough history. Tobacco consumption should be quantified:

$$\text{Total pack years} = \frac{\text{Number of cigarettes smoked/day}}{20} \times \text{number of smoking years}$$

Careful assessment of symptoms and the resulting disability should follow. Many patients modify their lifestyle and daily activities over many years to avoid shortness of breath and tend to minimize their symptoms, believing that advancing age or poor conditioning is the root cause. A series of probing questions is often required to uncover the true extent of the breathing difficulty and exercise curtailment that the patient experiences. Studies have confirmed that even patients with mild spirometric abnormalities may have significant symptoms and disability (32). The severity of breathlessness is usually assessed by determining the magnitude of the task (or daily activity) required to precipitate the breathing discomfort. The Panel advocates use of the Medical Research Council (MRC) dyspnea scale (33) to assess shortness of breath and disability in COPD (Figure 3, Table 3). Recent studies have shown that this simple scale can help identify patients with a poor quality of life (34). Moreover, MRC ratings provide prognostic information on survival with COPD (35). In conjunction with spirometry (Table 4), MRC ratings can help stratify disease severity and may be the most practical option for the general practitioner.

The history should also include an assessment of the frequency and severity of exacerbations because this information may guide treatment choices. Other important details that should be extracted are occupational exposures to other lung irritants, family history of COPD, or the presence of other chronic respiratory disease. The history should include an inquiry regarding symptoms that suggest other common comorbidities (ie, heart and circulatory diseases, anxiety and depression). The appropriateness of current medical treatment should be reviewed.

Physical examination: Physical examination of patients with COPD, although important, is not usually diagnostic and even careful physical examination can underestimate the presence of significant air flow limitation. With more advanced disease, signs of lung hyperinflation, right heart failure and generalized muscle wasting may be evident.

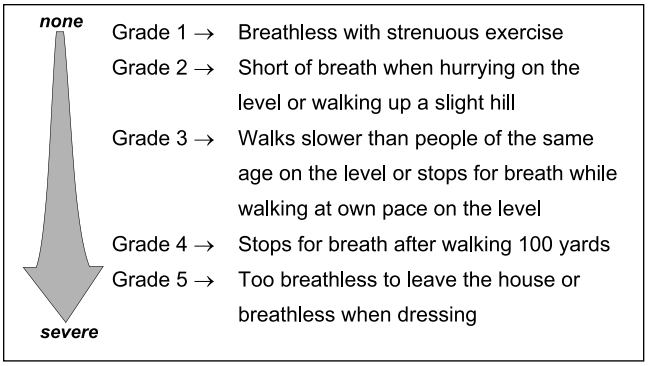

Figure 3) *The Medical Research Council dyspnea scale is used to assess shortness of breath and disability in chronic obstructive pulmonary disease. Reproduced from reference 33*

TABLE 4
Chronic obstructive pulmonary disease (COPD) classification by lung function

COPD stage	Spirometry
At risk	Normal spirometry, chronic symptoms
	$FEV_1/FVC \geq 0.7$ and/or $FEV_1 \geq 80\%$ predicted
Mild	FEV_1 60% to 79% predicted, $FEV_1/FVC < 0.7$
Moderate	FEV_1 40% to 59% predicted, $FEV_1/FVC < 0.7$
Severe	FEV_1 <40% predicted, $FEV_1/FVC < 0.7$

FEV_1 Forced expiratory volume in 1 s; FVC Forced vital capacity

Investigations: Pulmonary function testing remains the best objective measurement of pulmonary impairment. Chest x-rays are not diagnostic for COPD, but are often required to rule out comorbidities. This also applies to high resolution computed tomography (CT) scanning, which is not routinely required. Arterial blood gas measurements should be offered to patients with an FEV_1 of less than 40% predicted (if they have low arterial oxygen saturation on oximetry) or to patients in whom respiratory failure is suspected.

Stratifying disease severity in COPD

Most existing paradigms for the stratification of disease severity use the FEV_1 (36,37). None of these have been validated and there is no consensus as to which stratification system should be used. The Panel believes that an ideal system would use a composite index with evaluation in the domains of impairment, disability and handicap. FEV_1 measurement,

TABLE 5
Clinical differences between asthma and chronic obstructive pulmonary disease (COPD)

	Asthma	COPD
Age of onset	Usually < 40 years	Usually > 40 years
Smoking history	Not causal	Usually > 10 pack-years
Sputum production	Infrequent	Often
Allergies	Often	Infrequent
Disease course	Stable (with exacerbations)	Progressive worsening (with exacerbations)
Spirometry	Often normalizes	Never normalizes
Clinical symptoms	Intermittent and variable	Persistent

while necessary for diagnostic purposes and for follow-up of the disease, correlates poorly with symptom intensity, exercise capacity and quality of life (26,34). Moreover, physicians rarely rely on FEV_1 thresholds to make therapeutic decisions. For these reasons, the Panel believes that management decisions should be based on an assessment of dyspnea and disability on an individual basis, rather than on spirometry alone. The Panel encourages the use of the MRC scale for dyspnea and disability assessment (33). A simple stratification system, where severity is based on the MRC grade, is provided in Table 3. Grade 0 refers to asymptomatic smokers or to patients who have chronic productive cough, but who do not yet meet spirometric criteria for diagnosis. These patients are at risk for developing overt COPD in the future. Such patients should receive regular follow-up with annual spirometry. Therapy would be expected to escalate from MRC grade 2 through to grade 5. Patients with an MRC score of 2 or greater have significant disability and will benefit from effective treatment. Patients with an MRC grade of 5 are greatly disabled and require a more intensive comprehensive management strategy to optimize outcomes.

Differential diagnosis of COPD

COPD versus asthma: In most instances, physicians can readily differentiate between COPD and asthma (Table 5). However, in a small proportion of patients (eg, those with chronic asthma who are smokers), diagnostic differentiation can be challenging and may require specialist assistance. COPD patients generally have a later age of onset of symptoms and have a significant smoking history. In COPD, symptoms are chronic and slowly progressive over years, whereas in asthma, symptoms of shortness of breath are more intermittent and less likely to be associated with progressive disability. When patients exhibit the clinical features outlined above, together with a demonstration of persistent airway obstruction (ie, FEV_1/FVC ratio less than 0.7, FEV_1 less than 80% predicted) in response to a trial of acute bronchodilator therapy, this strongly suggests the diagnosis of COPD.

COPD – Differential diagnosis of chronic breathlessness: Other conditions included in the differential diagnosis of older patients presenting with progressive breathlessness include cardiovascular conditions, pulmonary vascular disease (pulmonary emboluses), severe deconditioning, obesity, anemia, interstitial lung disease, and rarely, neuromuscular disease. Patients with advanced COPD often have several comorbidities.

When to refer to a specialist

Family physicians have a primary role in the management of COPD. They are responsible for the early identification and diagnosis of COPD and have a major role in education and disease prevention, including smoking cessation. They initiate drug treatment, manage exacerbations, and are primarily responsible for patient follow-up and end-of-life care. The Panel believed that referral to a specialist may be appropriate when there is uncertainty over the diagnosis; symptoms are severe or disproportionate to the level of obstruction; there is an accelerated decline of function (FEV_1 decline of 80 mL or more per year over a two-year period); and the onset of symptoms occurs at a young age (less than 40 years). Specialists can also assist in the assessment and management of patients who fail to respond to combined bronchodilator therapy, or those who require pulmonary rehabilitation, or an assessment for oxygen therapy. Other possible reasons for specialist assistance are for the management of patients with severe or recurrent exacerbations of COPD or patients with complex comorbidities. Patients with advanced disease may require specialist assessment for surgical intervention (ie, bullectomy, lung volume reduction surgery [LVRS], lung transplantation).

Comprehensive assessment of COPD patients with more advanced disease

It is now possible, with a reasonable degree of refinement, to comprehensively evaluate patients with COPD within the domains of physiological impairment (loss of anatomical structure or function); disability or activity restriction (lack of ability to perform an activity within the range considered normal); and handicap/participation restriction (ie, disadvantage caused by disability or impairment that limits fulfillment of a normal role). This assessment includes evaluation of symptom intensity (ie, the MRC scale) (33) and nutritional status (eg, body mass index, lean body mass), as well as full pulmonary function testing including lung volumes and diffusion capacity, arterial blood gas measurement and CT scanning, if indicated, to allow a better clinical characterization of the disease on an individual basis. Cardiopulmonary exercise testing (CPET) is increasingly used in the assessment of symptoms and disability in COPD. Recently, peak symptom-limited oxygen uptake during CPET has been shown to predict survival in patients with COPD, independent of age and FEV_1 (38). Moreover, exercise testing allows an evaluation of the integrative functions of the respiratory, cardiovascular, peripheral muscle, and metabolic systems. CPET may uncover unsuspected comorbidities in COPD, such as active ischemic heart disease and peripheral vascular disease, and assist in preoperative evaluation. It is now possible to evaluate peripheral muscle function in COPD (ie, strength and endurance testing, dual energy x-ray absorptiometry scans, and CT imaging); leg muscle dysfunction has been shown in several recent studies to contribute importantly to exercise intolerance and disability (2). Disease-specific quality of life questionnaires have proven validity for the purpose of epidemiological studies, but have limited use for assessment on an individual basis.

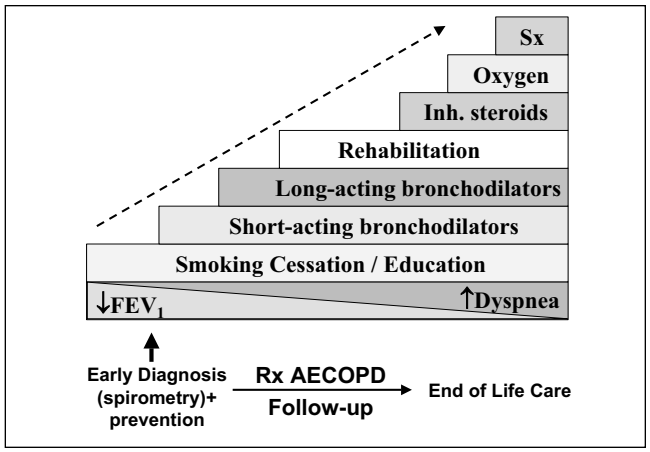

Figure 4) *A stepwise approach to the management of chronic obstructive pulmonary disease (COPD). FEV_1 Forced expiratory volume in 1 s; Inh Inhaled; Rx AECOPD Treatment of acute exacerbations of COPD; Sx Surgery (lung volume reduction surgery and transplantation)*

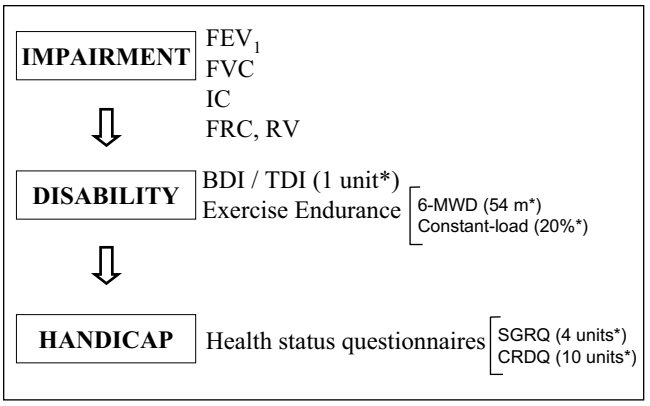

Figure 5) *Assessment of impairment, disability and handicap are part of a comprehensive evaluation of bronchodilator efficacy. *Clinically minimal important difference. BDI Baseline Dyspnea Index; CRDQ Chronic Respiratory Disease Questionnaire; FEV_1 Forced expiratory volume in 1 s; FRC Functional residual capacity; FVC Forced vital capacity; IC Inspiratory capacity; 6-MWD Six-minute walking distance; RV Residual volume; SGRQ St George's Respiratory Questionnaire; TDI Transition Dyspnea Index*

Specialized testing

Oral steroid reversibility testing: Previous meta-analyses suggest that a minority (10%) of patients with COPD show objective improvements in airway obstruction following a challenge of oral steroid therapy (39). Those who do respond well to oral steroids may have asthma. An improvement in the FEV_1 of greater than 20% or greater than 0.2 L is often regarded as indicating significant steroid reversibility. However, it is important for the practitioner to realize that the minimal degree of response to corticosteroids that needs to be considered to establish a diagnosis of asthma is not known. Furthermore, the role of steroid trials remains controversial, particularly because there is recent evidence that responses to short courses of oral steroid treatment do not reliably predict a long term clinical response to subsequent inhaled corticosteroids (ICS) therapy (40,41). Oral steroid trials (ie, prednisone, 0.5 mg/kg, for two to three weeks) may be indicated on an individual basis in patients with features of asthma (past or present medical history) who remain symptomatic despite maximal bronchodilator therapy and smoking cessation. It is reasonable to maintain patients on ICS who meet reversibility criteria or who experience symptom relief. However, the Panel believed that oral steroid reversibility testing is not indicated for the routine assessment of COPD.

Trial of inhaled steroid therapy: International guidelines (Global Initiative for Chronic Obstructive Lung Disease) have recently advocated maintenance of ICS therapy in patients with proven reversibility (ie, an increase in post bronchodilator FEV_1 of 12% above baseline or more than 200 mL) after six weeks to three months of ICS therapy (37). The Panel believed that such testing presents practical difficulties for many family physicians. Inhaled steroid reversibility therapy was not recommended by the Panel as a routine assessment, but such testing should be reserved for selected individuals, particularly for patients who remain significantly breathless despite optimal/maximal bronchodilators therapy.

MANAGEMENT OF COPD

The goals of management of COPD are as follows:

1. To prevent disease progression (smoking cessation);
2. To alleviate breathlessness and other respiratory symptoms;
3. To improve exercise tolerance;
4. To prevent and treat exacerbations;
5. To improve health status; and
6. To reduce mortality.

The Panel emphasized that all of these goals are achievable with integrated modern management of COPD. It is possible to effectively relieve shortness of breath and improve exercise capacity, even in advanced disease. Even modest improvements in these parameters are meaningful to the patient and can result in measurable improvements in their quality of life.

The management of COPD requires a step-wise approach, where therapy is escalated in accordance with the increasing severity of symptoms and disability (Figure 4). Smoking cessation and education that incorporates a self-management plan should be offered to all patients. Bronchodilator therapy should be prescribed to achieve maximum symptom control. Patients should be encouraged to exercise regularly to avoid deconditioning or, preferably, to enroll in a supervised pulmonary rehabilitation program. Some patients may benefit from the addition of ICS therapy. Supplemental oxygen and surgery are reserved for consideration in advanced disease.

It is essential, once the diagnosis has been made, that continuous follow-up of patients occurs with prompt and effective treatment of acute exacerbations. Patients with advanced symptomatic disease require a comprehensive management plan that includes effective end-of-life care.

ASSESSMENT OF THERAPEUTIC INTERVENTIONS IN CLINICAL TRIALS

The Panel comprehensively evaluated each therapeutic intervention in terms of its impact on parameters that reflect impairment; disability; and handicap (Figure 5).

Impairment

The traditionally measured end point in COPD is FEV_1. Spirometric measurements, including FEV_1, have the benefit of being widely available, reproducible and simple to obtain. Unfortunately, FEV_1 remains a relatively crude measure of small airways function and has been shown to correlate poorly with exercise tolerance and quality of life in individual COPD patients (26,42,43). Significant alleviation of breathlessness and improvement in exercise capacity can occur following interventions such as bronchodilators, oxygen therapy and exercise training, in the absence of changes in the FEV_1 (44,45). Currently, other measurements of impairment are being studied for the purpose of therapeutic evaluation (44-47), including assessment of lung hyperinflation (eg, inspiratory capacity, plethysmographic lung volumes) and peripheral muscle function.

Disability: Exercise testing

Exercise testing has been used in many studies to provide an objective measurement of the functional improvement offered by bronchodilators, oxygen, exercise training and surgery. Exercise testing can include many forms, ranging from relatively simple walk tests to more extensive cardiopulmonary exercise tests. Walk tests, such as the six-minute walk (where the patient is instructed to walk as far as possible within six minutes), require few resources and provide a reproducible measure of overall functional capacity. However, there is no consensus on what constitutes a clinically important improvement in walk distance. Studies have shown that the six- and 12-minute walk tests are responsive to interventions such as exercise training and surgery, but these field tests are often not sufficiently sensitive for the assessment of bronchodilator effectiveness compared with other forms of exercise testing (48). Constant load cycle exercise testing at 60% to 75% of the patient's maximal work capacity appears to be more sensitive than field tests for the purpose of bronchodilator evaluation (45,48).

Dyspnea assessment

Numerous instruments (scales) have been developed to quantify the impact of an intervention on shortness of breath. The MRC dyspnea scale is easy to administer and requires very little time (33). However, it is primarily a discriminative tool and may not be sensitive to change following various treatments because it was not intended to measure change over time.

Frequently used scales include the Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (which measure dyspnea and changes in dyspnea, respectively), and the Chronic Respiratory Disease Questionnaire (CRDQ) and St George's Respiratory Questionnaire (SGRQ) (which both measure quality of life) (49-51). The TDI measures changes in dyspnea from a baseline state, as assessed by BDI, and includes an assessment of the functional impairment, the magnitude of task and the magnitude of the effort (49). Each of these three components is scored on a scale from –3 to 3 (total –9 to 9). A total change of at least one unit is thought to be equivalent to a small but clinically significant change in chronic activity-related dyspnea. Improvements in the TDI score following exercise training average two to three units (49).

Handicap: Quality of life

The CRDQ is a 20-item questionnaire measuring dyspnea, fatigue and emotional function. The CRDQ is disease specific (to COPD) and administered by an interviewer (50). The dyspnea component is assessed by assigning a score of 1 to 7 (ranging from "extremely short of breath" to "not at all short of breath") to five individual-specific activities that caused breathlessness over the preceeding two weeks. The CRDQ was designed to evaluate the response to an intervention, with scores taken before and after. The consensus opinion is that an intervention producing a change of three points in the dyspnea domain (0.6 points per item) is the minimum required for a clinically significant reduction in dyspnea. A change of 10 points in the overall score (0.5 points per item) is considered to be clinically meaningful.

The SGRQ is a disease-specific (to asthma and COPD), self-administered questionnaire (51). A change in score by two units following an intervention is considered 'satisfactory' by patients, although the meaning of this is ambiguous. A change of 4.3 units is the average required for a treatment to be considered 'effective'.

Therapeutic evaluation in the office

A comprehensive evaluation of drug therapy in the domains of impairment, disability and handicap is currently reserved for clinical trial settings. Bronchodilator reversibility testing in the office or laboratory does not reliably predict the clinical response to bronchodilators in the long term on an individual patient basis. In clinical practice, the caregiver determines whether a bronchodilator has helped by asking the patient a few simple questions: "Did the new treatment help your breathing?" and, if the answer is affirmative, "In what way has it helped you?" If the patient responds that he/she can undertake a particular task with less breathlessness or for a longer duration since taking the drug, the caregiver is usually convinced of the drug's benefit. If the patient does not report any subjective benefit from taking a new bronchodilator medication, the caregiver may wish to alter the dosage, if appropriate, or advise the patient to discontinue the drug but perhaps recommence it if he/she experiences symptomatic deterioration after withdrawal of the drug. Assessing compliance is another factor in this circumstance.

EDUCATION

The Panel welcomed recent new initiatives for the provision of structured, disease-specific educational programs to COPD patients in Canada. Certified COPD educators will play a pivotal role in the success of chronic care plans for this population. The Panel strongly believed that a change in focus from an acute, 'reactive' care plan toward a sustained, 'proactive' integrated management plan is more appropriate for this chronic, disabling condition. Components of COPD education need to be individualized because they will vary with disease severity. Important educational components are outlined in Table 6. Education of COPD patients is aimed primarily at improving their coping skills to help them to control their disease and to live functional lives. Studies have shown that education alone is not associated with improved lung function or exercise performance (52). However, specific educational

TABLE 6
Components of a chronic obstructive pulmonary disease (COPD) educational program

Smoking cessation (level of evidence: 1A)
Basic information: Pathophysiology
Rationale for medical treatments
Effective inhaler technique
Self-management 'multicomponent' with case manager participation (level of evidence: 1A)
Coping skills development
Strategies to alleviate dyspnea
Decision making regarding acute exacerbations of COPD
Advanced directives and/or end-of-life issues
Identification of educational resources

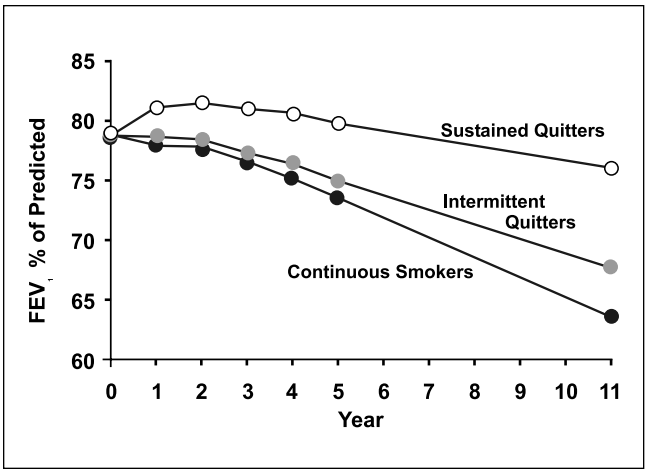

Figure 6) *Average post bronchodilator forced expiratory volume in 1 s (FEV_1) values expressed as a percentage of predicted normal values are shown over 11 years of study among continuing smokers, intermittent quitters and sustained quitters. Reproduced with permission from reference 58*

interventions, such as self-management programs and smoking cessation, have been shown to be effective (53,58).

Self-management plans in COPD

A number of studies are currently underway to evaluate the impact of various educational interventions in COPD. A recent randomized clinical trial conducted in Quebec evaluated the efficacy of a self-management program with supervision and support by a case manager in patients with moderate to severe COPD (53). Two hundred patients were recruited and randomly assigned to either usual care alone or usual care supplemented by a disease-specific self-management program. The program consisted of a flip chart designed for health educators and patient workbook modules detailing COPD management in all facets of the disease, including inhalation technique sheets and a plan of action. Patients were encouraged to increase their daily physical activity and to follow an exercise program. Patients also had monthly telephone follow-up by a trained health professional. The main outcomes were quality of life and health care usage at one year. Patients included in this study were, on average, 70 years old with an FEV_1 of 1 L. The main findings of this study were a marked reduction in the use of health care services and a cost saving in the intervention group. Health-related quality of life was also improved at four months but to a lesser degree than with pulmonary rehabilitation with a formal, supervised exercise training program. The results of this and other studies strongly demonstrate that providing self-management 'multicomponents' in the continuum of care may be beneficial in terms of reducing health care usage and the associated costs (level of evidence: 1A) (53-56). These benefits to the health system could potentially add to the patients' quality of life by avoiding hospitalization.

Recommendation

- Educational intervention of the patient and the family with supervision and support based on disease-specific self-management principles is valuable, and should be part of the continuum of optimal COPD management in Canada (level of evidence: 1A).

Smoking cessation

In 2000 to 2001, 25% of Canadians aged 12 years and over smoked, with the highest percentage of smokers (ie, 35%) in the 20- to 24-year-old cohort (57). Cigarette smoking is the single most important cause of COPD, and the greater the exposure, the greater the risk of developing airway obstruction. The accelerated decrease of the FEV_1 in susceptible smokers, compared with nonsmokers, will lead to clinically significant COPD in about 15% of smokers. Quitting smoking produces only a small improvement of the FEV_1 (58,59). However, the subsequent rate of decline returns to that of a nonsmoker, thus helping to avoid disability due to lung disease (Figure 6). Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and the only intervention that has been shown to slow its progression (level of evidence: 1A). Quitting will result in symptomatic relief of chronic cough, sputum expectoration, shortness of breath and wheezing, and will reduce the risk of cardiovascular disease and cancer of the lung and other organs. Although 46% of smokers try to quit each year, only about 7% are still abstinent one year later (60). The majority of smokers cycle through many relapses and remissions, reflecting the chronic nature of the dependence, or addiction, and, thus, not the failure of patients or clinicians (60).

At least 70% of smokers visit a physician each year and advice from a physician is quoted as an important motivator to quit (60). Advice from physicians (level of evidence: 1A), nonphysician health professionals (level of evidence: 2A), and individual and group counselling (levels of evidence: 1A) have all been shown to increase cessation rates. Discussing high-risk situations, developing coping skills and anticipating relapse all increase cessation rates (level of evidence: 2A) (60). The use of medication, including nicotine replacement therapy and the antidepressant bupropion, approximately doubles cessation rates (level of evidence: 1A) (60-62). There is insufficient evidence to support hypnosis or acupuncture in smoking cessation (level of evidence: 3C) (60).

TABLE 7
Effects of long-acting beta$_2$-agonists on chronic dyspnea, exercise endurance and health status

Author, year (Reference)	Drug/dosage	Study design	N	Outcome measure
Mahler, 1999 (265)	Salmeterol 42 µg bid	12 week, parallel	411	TDI: salmeterol 1 unit
	IB 36 µg qid			IB 1 unit
	Placebo			6-MWD: NS
				ΔFEV_1: NR*
ZuWallack, 2001 (89)	Salmeterol 42 µg	12 week, parallel	943	TDI: salmeterol 1.2±0.2 (±SE)
	Theophylline 100 mg			theophylline 1.1±0.2
	Salm + theo combination			salm + theo 1.9±0.2
Grove, 1996 (78)	Salmeterol 50 µg bid	4 week, parallel	29	12-MWD: +24 m (NS)
	Placebo			ΔFEV_1: 0.11 L
Boyd, 1997 (76)	Salmeterol 50 µg bid	6 week, parallel	674	6-MWD: +21 m (NS)
	Salmeterol 100 µg bid			ΔFEV_1: NR both dosages*
Jones, 1997 (266)	Salmeterol 50 µg bid	16 week, parallel	283	SGRQ: salmeterol 50*
	Salmeterol 100 µg bid			salmeterol 100 NS
	Placebo			placebo NS
Rennard, 2001 (267)	Salmeterol 42 µg bid	12 week, parallel	405	SGRQ: salmeterol 10.3
	IB 36 µg qid			IB 9.2
	Placebo			placebo 6.8
Dahl, 2001 (74)	Formoterol 12 µg bid	12 week, parallel	780	SGRQ:
	Formoterol 24 µg bid			formoterol 12 Δ = –5.1*
	IB 40 µg qid			formoterol 24 Δ = –6.1*
	Placebo			IB Δ = NS

**P<0.05 significant improvement. bid Twice daily; Δ Change; CRDQ Chronic Respiratory Disease Questionnaire; IB Ipratropium bromide; MWD Minute walk distance; NR Not reported; NS Not significant; Salm Salmeterol; SGRQ St George's Respiratory Questionnaire; Theo Theophylline; TDI Transition Dyspnea Index*

Recommendation

- Even minimal educational interventions, lasting less than three minutes, should be offered to every smoker with the understanding that more intensive pharmaceutical therapy, resulting in the highest quitting rates, should be used whenever possible (level of evidence: 1A).

VACCINATIONS

COPD patients infected with influenza have a significant risk of requiring hospitalization. Annual influenza vaccination reduces morbidity and mortality from the disease by as much as 50% in the elderly, and reduces the incidence of hospitalization by as much as 39% in patients with chronic respiratory conditions (63,64).

The benefit of pneumococcal vaccination in COPD patients is less well established. Reports state that the vaccine has an efficiency in COPD patients of up to 65%, although a reducing effect on the frequency of acute exacerbations of COPD (AECOPD) has yet to be established (65).

Recommendation

- An annual influenza vaccination is recommended for all COPD patients who do not have a contraindication (level of evidence: 2A).
- The Panel recommends that all patients with COPD be given the pneumococcal vaccine at least once in their lives, and that consideration be given to repeating the vaccination in five to 10 years in high-risk patients (level of evidence: 3C).

PHARMACOTHERAPY IN COPD

Bronchodilator therapy

Bronchodilators currently form the mainstay of pharmacological therapy for COPD. Bronchodilators work by decreasing airway smooth muscle tone, thus improving expiratory flow and lung emptying with each breath. Although administration can be via both inhaled and oral routes, inhaled therapy is preferable to oral therapy because inhaled drugs target the airway directly and are less likely to cause systemic adverse effects. There are three major classes of bronchodilators available for use in COPD: anticholinergics, beta$_2$-agonist drugs and methylxanthines (which are administered orally). All three classes include drugs that are short acting or long acting. In addition, bronchodilators can be combined with one another in one formulation (eg, salbutamol and ipratropium bromide combination products) and can be combined with ICS (eg, formoterol and budesonide, and salmeterol and fluticasone combination products).

TABLE 8
Effects of tiotropium bromide on chronic dyspnea and health status

Author, year (reference)	Tiotropium dosage	Study design	n	TDI	ΔQoL
Casaburi, 2002 (80)	18 µg od (vs placebo)	1 year, parallel	921 (3:2 ratio)	0.8 to 1.1*	SGRQ >3* (>4 for symptoms*)
Vincken, 2002 (81)	18 µg od (vs IB 40 µg qid)	1 year, parallel	535 (2:1 ratio)	0.90*	SGRQ 3.3* (4.28 for impact*)
Donohue, 2002 (83)	18 µg od (vs SAL 50 µg bid or placebo)	6 months, parallel	623	0.78* vs SAL	SGRQ 1.6
				1.02* vs placebo	SGRQ 2.7*

**P<0.05 Significant difference. ΔQoL Change in quality of life; bid Twice daily; IB Ipratropium bromide; qid four times daily; SAL Salmeterol; SGRQ St George's Respiratory Questionnaire; TDI Transition Dyspnea Index*

The ideal bronchodilator would be well tolerated and demonstrate sustained improvement in spirometry, lung hyperinflation, exercise performance, dyspnea and quality of life in all patients with COPD. The committee examined all of these outcomes to provide a comprehensive evaluation of each bronchodilator. When reviewing the existing literature, it becomes evident that there is significant heterogeneity in the methodology and results of clinical trials involving bronchodilators in COPD. The evidence supporting the use of three classes of bronchodilators in COPD, as well as the combination products, is summarized below.

- Short-acting bronchodilators, both anticholinergics and beta$_2$-agonists, have been shown to improve pulmonary function, dyspnea and exercise performance in COPD (45,66-71). They have not been shown to have a consistent impact on quality of life. Individual responses to the different classes are variable.

- The use of short-acting anticholinergic and beta$_2$-agonists together produces superior bronchodilation than either drug does alone and may be more convenient for some patients. However, the combination product has not been shown to be superior in terms of dyspnea alleviation, exercise performance or quality of life (72,73).

- Long-acting beta$_2$-agonists (LABAs) offer more sustained improvements in pulmonary function, chronic dyspnea and quality of life than short-acting bronchodilators. However, the effects of LABAs on exercise performance have been inconsistent (74-79) (Table 7).

- The new, long-acting anticholinergic, tiotropium bromide, has been shown to have more sustained effects on pulmonary function, chronic activity-related dyspnea and quality of life compared with regular dose ipratropium bromide (40 µg four times daily) and placebo (80-83). Tiotropium has also been shown to reduce exacerbation and hospitalization rates. Tiotropium is a once-daily medication and, therefore, compliance with therapy may also be improved with this preparation (Table 8).

- While theophyllines are relatively weak bronchodilators, they offer modest improvements in pulmonary function, dyspnea and exercise performance. The addition of oral theophyllines to inhaled bronchodilator therapy may offer additive benefits in some patients (84-89).

Recommendation

- For patients with symptoms that are only noticeable with exertion and who have relatively little disability, initiation of therapy with either a short-acting beta$_2$-agonist as needed (or a regular anticholinergic or combination anticholinergic and/or beta$_2$-agonist) is acceptable. The choice of first-line therapy in mild symptomatic COPD should be individualized, and based on clinical response and tolerance of side effects (level of evidence: 1A).
- For patients whose symptoms persist despite reasonable short-acting bronchodilator therapy, a long-acting bronchodilator should be used. Recommended long-acting bronchodilators include the anticholinergic preparation tiotropium (18 µg once daily), or alternatively, a LABA (formoterol 12 µg twice daily or salmeterol 50 µg twice daily) may be used (level of evidence: 1A). Short-acting beta$_2$-agonists may be used as needed for immediate symptom relief.
- For patients with moderate to severe persistent symptoms and exercise intolerance, a combination of tiotropium 18 µg once daily and an LABA (ie, formoterol 12 µg twice daily or salmeterol 50 µg twice daily) is recommended to maximize bronchodilation, although it should be noted that the results of ongoing studies on the effect of this combination on various health outcomes are not yet available (level of evidence: 3A). Short-acting beta$_2$-agonists can be used as needed for immediate symptom relief.
- In patients with severe symptoms despite use of both tiotropium and an LABA, a long-acting preparation of oral theophylline may be tried, although monitoring of blood levels, side effects and potential drug interactions is necessary (level of evidence: 3B).

Adverse effects of anticholinergics: Inhaled anticholinergic drugs are generally well tolerated. A bitter taste is reported by some using ipratropium. Occasional prostatic symptoms, with urinary retention, have been reported. The use of wet nebulizer solutions with a face mask can precipitate glaucoma if the drug gets directly into the eye. In clinical trials, tiotropium has been associated with a dry mouth in 12% to 16% of patients; however, less than 1% of patients withdrew from the trial due to this side effect. Urinary retention occurred in 0.73% of patients taking tiotropium and urinary tract infection occurred in 7.3% of patients taking tiotropium compared with 5.1% of patients taking placebo (80,81).

TABLE 9
Effects of inhaled corticosteroids: Long term placebo-controlled studies

Efficacy variables	ISOLDE (2000)	EUROSCOP (1999)	Copenhagen (1999)	Lung Health Study (2000)
Primary				
↓ FEV_1	No effect	No effect	No effect	No effect
Secondary				
Symptoms	NR	NR	No effect	~↓ dyspnea
Exacerbations	↓25%	NR	No effect	NR
Quality of life	↑	NR	NR	No effect
MD visits	NR	NR	NR	↓
Bronchial responsiveness	NR	NR	NR	↓

↓ Decrease; ↑ Increase; EUROSCOP European Respiratory Society study on chronic obstructive pulmonary disease; FEV_1 Forced expiratory volume in 1 s; ISOLDE Inhaled Steroids in Chronic Obstructive Lung Disease in Europe; MD Medical doctor; NR Not reported

Adverse effects of beta$_2$-agonists: Inhaled beta$_2$-agonists are generally well tolerated. The most common adverse effects involve the cardiovascular system and the central nervous system. Cardiovascular effects include tachycardia, palpitation and flushing. Extrasystoles and atrial fibrillation may also be seen. In patients with coronary artery disease, beta$_2$-agonists may induce angina. Central nervous system effects include irritability, sleepiness and tremor. Other adverse effects of beta$_2$-agonists may include gastrointestinal upset, nausea, diarrhea, muscle cramps and hypokalemia (79).

Bronchodilator therapy – Practice points: Studies that have examined the FEV_1 response to increasing dosages of short-acting bronchodilators (short-acting beta$_2$-agonists and anticholinergics) have indicated a relatively flat dose-response curve (90,91). Therefore, evidence for a definitive recommendation for the use of increased doses of these drugs is lacking. Clinical experience, however, has shown that some individuals appear to achieve greater symptomatic responses to higher doses of short-acting bronchodilators. Similarly, the nebulized route of delivery for short-acting bronchodilators has not been shown to be superior to the metered-dose inhaler (MDI) delivery route in terms of FEV_1 response (92). However, some patients express personal preference for wet nebulization and report greater symptomatic benefits. Consequently, the nebulized route may be considered in the treatment of AECOPD or in clinically stable patients with severe breathlessness who have profound lung overinflation and inspiratory muscle weakness, and who are unable to breath-hold for more than a few seconds.

Available information on the pharmacokinetics of the long-acting anticholinergic tiotropium suggest that the addition of short-acting anticholinergics (ipratropium bromide, combination ipratropium bromide and salbutamol) should not result in additional benefits in terms of increased bronchodilation but may, instead, predispose patients to significant adverse effects (93).

Corticosteroids

Oral corticosteroids: There has been no long term, randomized control trial examining the effects of oral corticosteroids alone. However, several short term trials have been reported over the last 50 years. Callahan et al (39) reported a meta-analysis based on 15 studies meeting pre-established quality criteria in 1991. Improvement of at least 20% of the FEV_1 from baseline was set as the clinically meaningful difference. It was estimated that only 10% of patients with stable COPD benefit from oral corticosteroids based on this operational definition (95% CI 18%). A recent study by Rice et al (94) showed that discontinuation of chronic oral corticosteroid treatment in patients with stable COPD did not cause a significant increase in COPD exacerbations. Currently, we have no reliable, simple clinical or laboratory parameters to identify the minority of patients who might show a benefit. Only the baseline eosinophil count in induced sputum has been shown to significantly correlate with reversibility of airway obstruction following treatment with oral corticosteroids (95-97) (level of evidence: 3B). The potential utility of this test in clinical practice needs further assessment.

Recommendation

- The Panel believes that long term treatment with oral corticosteroids should not be used in COPD, given the absence of benefit and the high risk of adverse systemic effects (level of evidence: 1E).

Adverse effects of oral steroids: The benefits of maintenance oral corticosteroid therapy must be weighed against the risk of adverse events. Adverse events are numerous and include adrenal suppression, osteoporosis, cataract formation, dermal thinning, muscle weakness, hypertension, diabetes, psychosis and hyperadrenocorticism (98-102).

ICS: Despite the controversy over ICS in COPD, prescription rates of this drug continue to increase in Canada and elsewhere. Examination of a recent Canadian health care database consisting of a cohort of 3768 physician-diagnosed, elderly COPD patients revealed that the annual percentage of patients filling prescriptions for inhaled steroids climbed from 42.2% in 1992 to 53.1% in 1995 (103).

Short term studies examining the effects of ICS on the inflammatory process in COPD have yielded inconsistent results (97,104-106). Several studies have shown that ICS did not appear to have consistent effects on FEV_1 symptoms, exercise capacity and health-related quality of life in patients with severe COPD (107). A study by Paggiaro et al (108) found that in patients with chronic bronchitis and mild air flow obstruction (who had a history of at least one exacerbation per year for the past three years), ICS therapy significantly reduced the severity, but not the number, of exacerbations over this time period.

Long term studies on the effects of ICS: To date, four major studies on ICS have been conducted: the European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP) (109); Copenhagen City Heart study (110); Inhaled Steroids in Chronic Obstructive Lung Disease in Europe (ISOLDE) study (40); and the Lung Health Study (111) (Table 9). All of these randomized clinical trials have not been able to show any benefit on the relentless decline in lung function characteristic of COPD (level of evidence: 1E). The EUROSCOP and Copenhagen studies were conducted in patients with mild disease. There were no treatment effects on respiratory symptoms or the frequency of exacerbations. The

Lung Health study was undertaken in patients with moderate COPD. Here, ICS treatment resulted in a reduction in respiratory symptoms, hyper-reactivity and hospitalization for respiratory conditions. In the ISOLDE study, patients with severe COPD had a significant reduction in acute exacerbation rates (by 25%) and rate of health status decline. A meta-analysis by Alsaeedi et al (107) selected nine randomized placebo-controlled trials. They were able to demonstrate an overall reduction of COPD exacerbations of 30% (RR 0.70; 95% CI 0.58 to 0.84) in patients treated with ICS.

Recommendation

- In contrast to asthma, ICS should not be used as first-line medication in COPD because no consistent effects have been demonstrated on airway inflammatory cells and related inflammatory mediators (level of evidence: 1D).
- Regular use of high dose ICS alone should only be considered in patients with moderate to severe COPD who have recurrent, acute exacerbations (ie, three exacerbations or more per year, especially those requiring the use of oral corticosteroids) (level of evidence: 1A).
- The Panel further suggested that the potential for limited benefits in many patients contrasted sharply with the high likelihood of adverse effects when ICS are used in high doses for prolonged periods of time, particularly in the elderly (level of evidence: 3A).

Adverse effects of ICS: Adverse effects of ICS include dysphonia and oral candidiasis (112-114). ICS in doses greater than 1.5 mg/day of beclomethasone equivalent may be associated with a reduction in bone density (115,116). Long term high doses of ICS are associated with posterior subcapsular cataracts, and, rarely, ocular hypertension and glaucoma (117-119). Skin bruising is also common with high dose exposure (40,109,111).

TABLE 10
Effects of inhaled corticosteroids (ICS) and long-acting beta$_2$-agonist (LABA) combination therapy on forced expiratory volume in 1 s (FEV$_1$), health status and exacerbation rate: Estimated differences at study endpoint

Author (reference): Outcome measure	C vs placebo	C vs LABA	C vs ICS
Mahler (120)			
Pre-dose FEV$_1$	159*	67*	54*
Post-dose FEV$_1$	231*	40	129*
Calverley (121)			
Pre-dose FEV$_1$	133†	73†	95†
Post-bronchodilator FEV$_1$	76†	48*	31*
Szafranski (122)			
Post-dose FEV$_1$	150†	10	90†
Mahler (120)			
CRDQ	5.3*	1.6	4.8*
Calverley (121)			
SGRQ	–2.2†	–1.1	–1.4
Szafranski (122)			
SGRQ	–3.9*	–0.3	–2.0
Mahler (120)			
Exacerbation rate	No SD	No SD	No SD
Calverley (121)			
Exacerbation rate	–25%†	–7%	–7%
Exacerbations requiring oral corticosteroids	–40%†	–15%	–7%
Szafranski (122)			
Severe exacerbation rate	–24%*	–23%	–11%
Exacerbations requiring oral corticosteroids	–31%*	N/A	N/A

**P<0.05; †P<0.001. C Combination products; CRDQ Chronic Respiratory Disease Questionnaire; SD Significant difference; SGRQ St George's Respiratory Questionnaire*

Combined ICS and LABAs

Two combination ICS and beta$_2$-agonist products are currently available in Canada (fluticasone and salmeterol, and budesonide and formoterol). To date, three published randomized control trials have investigated the combination products in COPD (120-122). Two of these studies (120,121) evaluated a 50/500 µg formulation of the fluticasone and salmeterol combination product, and a third study (122) evaluated the 6/200 µg formulation of the formoterol and budesonide combination product (Table 10). Patients enrolled in these studies had an average FEV$_1$ of 1 L to 1.4 L. All three studies had similar designs, randomly assigning patients to the placebo, the combination or one of the two components at the same dose as the combination. Because LABAs have been proven in previous clinical trials to result in improvements in FEV$_1$, dyspnea and quality of life compared with placebo, the Panel believed that the real comparison of interest for the combination product studies is not the comparison with the placebo but the comparison of the results seen with the combination products and the LABA or the ICS component alone.

Lung function: All three studies indicated that the combined inhaled steroid and LABA preparation might be superior to either drug alone in terms of improving pulmonary function. The mean improvement in FEV$_1$ with combination products compared with LABAs is on the order of 40 mL to 75 mL, and with inhaled steroids is on the order of 30 mL to 130 mL. The clinical significance of these small improvements in FEV$_1$ is difficult to interpret (120-122).

Dyspnea: In all three studies, the inhaled steroid plus LABA combination significantly improved dyspnea (measured by the TDI or patient diaries) relative to placebo. However, there were no consistent effects on dyspnea seen when comparing the inhaled steroid plus LABA combination to the LABA treatment alone (120-122).

Health status: In the Mahler study (120), the CRDQ score was used to measure quality of life. The combination treatment resulted in clinically important increases from baseline and in the mean overall CRDQ score, compared with placebo, but not with the salmeterol group. In the Calverley (121) study, the difference in the SGRQ total score was not significantly greater for the fluticasone plus salmeterol group over the salmeterol group alone. However, there were statistically significant differences for fluticasone plus salmeterol over salmeterol alone in the symptom domain and activity domain of the SGRQ. In the Szafranski (122) trial, the combination was supe-

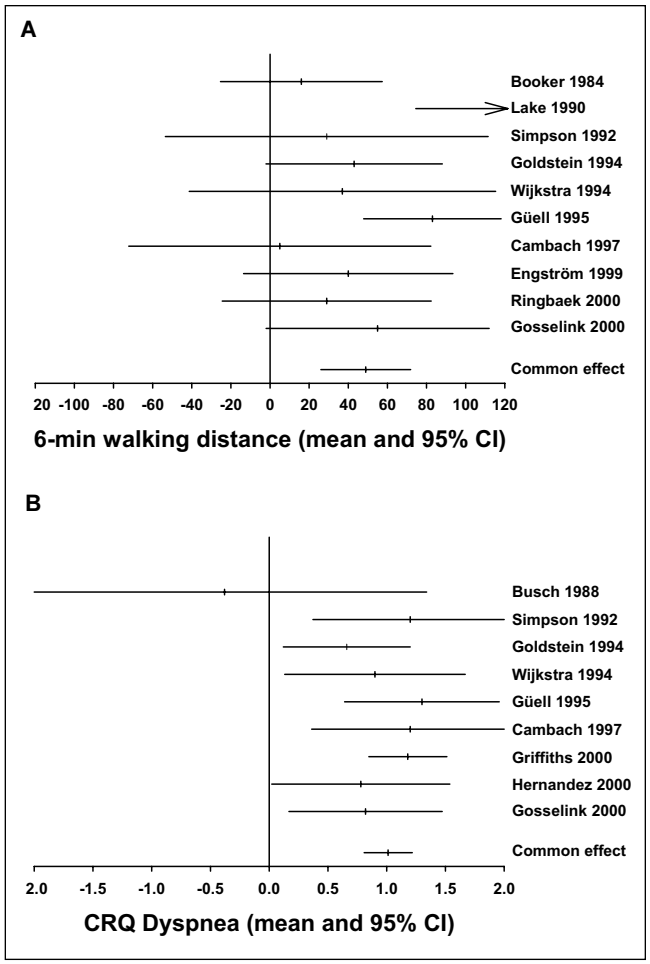

Figure 7) A *The effect of exercise training on functional exercise capacity in chronic obstructive pulmonary disease (COPD) (overall n=444).* **B** *The effect of exercise training on health status in COPD (overall n=519). CRQ Chronic Respiratory Disease Questionnaire. Reproduced with permission from reference 124*

rior to placebo in terms of the SGRQ score, but over the 12 months of the study, the combination was not superior to either formoterol or ICS alone (120-122).

Exercise: Exercise tolerance was not reported in any of the studies.

Exacerbations and hospitalizations: In all three studies (120-122), the combination products significantly decreased AECOPD and hospitalizations relative to placebo, compared with inhaled steroids alone. In the Szafranski et al study (122), the combination product was superior to the LABA component alone in terms of reduction of AECOPD.

Summary: To date, no studies have tested the effects of combined ICS and LABA therapy in patients who were receiving maximal and/or optimal bronchodilation. This information is required for any definitive recommendation with respect to the role of ICS and LABA products for the enhanced control of dyspnea. Studies that are designed to compare the effects of ICS and LABA products with their monocomponents on dyspnea, exercise performance and health status as primary outcome measures are urgently needed.

Recommendation

- The Panel suggests that in symptomatic patients with more advanced disease who experience frequent exacerbations, ICS and LABAs should be prescribed as a matter of convenience for patients already receiving LABAs and ICS separately (level of evidence: 3A).
- The Panel believes that in patients who remain breathless despite optimal bronchodilator therapy, the addition of ICS and LABA could be considered for enhanced symptom relief, on an individual basis, but there is not sufficient evidence for a general recommendation at this time (level of evidence: 3A).

PULMONARY REHABILITATION

Patients with COPD who experience activity-related shortness of breath often reduce activity levels to avoid precipitating respiratory discomfort. This reduced activity over time eventually leads to severe generalized skeletal muscle deconditioning to a degree where even minor activity provokes shortness of breath. Modern pharmacotherapy increases exercise capabilities, but patients who persist in a sedentary lifestyle may not realize their full potential in terms of enhancing exercise performance. For these reasons, the Panel suggested that all COPD patients should be encouraged to maintain an active lifestyle to avoid this downward disability handicap spiral that can lead to social isolation.

Benefits of pulmonary rehabilitation

A meta-analysis of 23 randomized controlled trials in COPD showed that pulmonary rehabilitation significantly improved dyspnea, exercise endurance and quality of life compared with standard care (123,124) (Figure 7). These improvements in dyspnea and exercise performance are largely attributable to the exercise training component of the rehabilitation program because education alone has no effect on these parameters (52). Recent studies have provided a solid physiological rationale for many of the improvements of exercise training, particularly relief of dyspnea and improved exercise capacity. The physiological benefits of exercise training in COPD include improved strength and endurance of ventilatory muscles; improved breathing pattern and ventilatory capacity; improved strength and endurance of peripheral locomotor muscles with increased aerobic capacity; and cardiovascular training effects that are measurable in some patients following training (125-127). Psychosocial support in the rehabilitation setting is also a key contributor to the success of such programs.

Recent randomized controlled trials with long term follow-up of patients after rehabilitation have shown a trend toward decreased hospital days, fewer exacerbations and more efficient primary care use (52,128-130). In one study (130), patients who successfully completed a six-month rehabilitation program had a significant reduction in mortality rate compared with those receiving standard care without rehabilitation.

Cost effectiveness

Three large randomized controlled trials examined the direct and indirect costs related to health care delivery in patients

undergoing rehabilitation compared with a control group who received standard care (53,131,132). The studies concluded that the entire expenses associated with pulmonary rehabilitation were completely offset by the reduction in health utilization costs; the cost effectiveness profile was better for outpatients compared with inpatient pulmonary rehabilitation; and pulmonary rehabilitation is highly cost effective compared with many other therapeutic interventions in chronically disabled patients (eg, hemodialysis or hip replacement).

Long term effects of pulmonary rehabilitation

The benefits of pulmonary rehabilitation (improved dyspnea, activity level and quality of life) are usually sustained for several months after the end of the exercise program (52,128,133-136). However, initial improvement in these parameters is progressively lost after stopping exercise, highlighting the importance of incorporating a carefully supervised home-based maintenance exercise program. AECOPD are recognized as having a negative influence on exercise maintenance programs in this population.

Who to refer to pulmonary rehabilitation

Criteria for referral to a pulmonary rehabilitation program include clinically stable, symptomatic COPD; reduced activity levels and increased dyspnea despite pharmacological treatment; no evidence of active ischemic, musculoskeletal, psychiatric or other systemic disease; and sufficient motivation for participation.

Adjuncts to exercise training

Specific inspiratory muscle training (137,138), upper extremity training (139,140), nutritional supplementation (141,142), alone or combined with anabolic steroids (143), and exercise training are being evaluated as adjuncts to rehabilitation. There is currently no conclusive evidence that these are effective, but all of these interventions require further systematic study.

Access to pulmonary rehabilitation in Canada

In 1999, it was estimated that there were only 36 pulmonary rehabilitation programs in Canada, serving less than 1% of the Canadian COPD population (144). The Panel agreed that strategies should be developed to improve the availability of pulmonary rehabilitation, deliver rehabilitation at a lower cost per patient and implement self-monitored, but supervised, home-based rehabilitation programs.

OXYGEN THERAPY FOR COPD

The survival benefit of domiciliary oxygen has been documented by two large randomized controlled trials, the MRC and the Nocturnal Oxygen Therapy study groups (145,146). Both studies were conducted in hypoxemic COPD patients (with a partial pressure of arterial oxygen [PaO_2] of 60 mmHg or less), most of whom were male. Taken together, these trials demonstrated that the benefits from long term oxygen therapy (LTOT) are dose-dependent: the longer the exposure to supplemental oxygen, the larger the benefits in terms of survival.

Recommendation

- Long term continuous oxygen (15 hours/day or more to achieve a saturation of 90% or greater) should be offered to patients with stable COPD with severe hypoxemia (PaO_2 of 55 mmHg or lower), or when PaO_2 is less than 60 mmHg in the presence of bilateral ankle edema, cor pulmonale or a hematocrit of greater than 56%.

Quality of life was not quantitatively derived, although an improved sense of well being and improved neuropsychiatric function were reported. Other studies addressing the effects of oxygen therapy during exercise and pulmonary rehabilitation did not demonstrate significant improvements in measures of quality of life. A relatively recent, reasonably sized, unblinded randomized controlled trial of domiciliary oxygen conducted in COPD patients with mild hypoxemia (PaO_2 56 mmHg to 65 mmHg) failed to demonstrate a survival benefit (147). However, the oxygen administration might have been suboptimal (13.5 hours/day on the average, without any increase in flow rate during sleep or activity). Two smaller randomized controlled trials (148,149) did not document increased survival in COPD patients with nocturnal desaturation and daytime PaO_2 levels above 60 mmHg.

Sleep

Nocturnal oxygen desaturation in COPD has been suggested to increase mortality (148,149). It has also been associated with poor sleep quality as indicated by reduced sleep time, increased sleep stage changes and increased arousal frequency (150). Nocturnal oxygen therapy has not been shown to increase survival in COPD patients with 'isolated' nocturnal oxygen desaturation, nor was it shown to be consistently effective in improving sleep quality in these patients (151,152). Because obstructive sleep apnea is common, there is a high likelihood that a few patients will have both conditions.

Existing evidence does not support the prescription of nocturnal oxygen therapy for COPD patients with 'isolated' nocturnal desaturation. Obstructive sleep apnea and chronic hypercapnic respiratory failure should be separated from COPD because they represent different diagnostic categories with alternative approaches to management. The panel is mindful that many physicians prescribe nocturnal oxygen therapy for patients with severe or progressive nocturnal desaturation. The following recommendation is consistent with current practice.

Recommendation

- Nocturnal oxygen therapy may be considered if desaturation occurs for protracted periods (eg, more than 30% of the time in bed at an arterial oxygen saturation of less than 88%) or in the presence of pulmonary hypertension, cor pulmonale or other associated medical conditions that might influence survival (level of evidence: 3B).

Exercise and dyspnea

Moderate hyperoxia (fraction of inspired oxygen of 0.4 to 0.6, which achieves a PaO_2 of greater than 200 mmHg) during

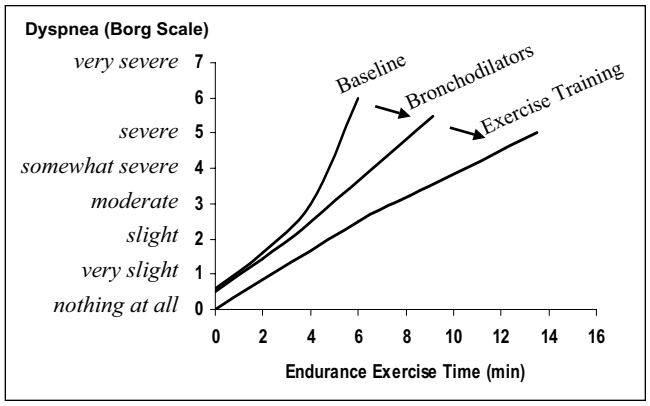

Figure 8) *Plots of exertional dyspnea intensity (Borg Scale) against endurance time using a constant work rate exercise test illustrate the cumulative effects of a stepwise approach to therapy in chronic obstructive pulmonary disease*

submaximal exercise testing increases exercise time, reduces exercise minute ventilation and dynamic lung hyperinflation, and may delay respiratory muscle dysfunction in patients with moderate to severe COPD. Improved exercise performance correlated with decreased lactate production (153-155). Supplemental oxygen administered via nasal cannulae diminishes transient exercise hypoxemia and has been associated with modest (10%), variable improvements in exercise capacity and improved dyspnea scores (156-158). In randomized controlled trials in which subjects underwent supervised exercise rehabilitation with oxygen or with air, this transient improvement did not result in a significant between-group difference in exercise tolerance, dyspnea scores or health-related quality of life (159,160). One study of oxygen versus air during home activities did not identify between-group differences (161). The degree of improvement post rehabilitation could not be predicted from lung function and did not correlate with the severity of exercise-induced desaturation (158,160,162).

Recommendation

- Patients with incapacitating dyspnea and reduced ventilatory and exercise capacity may benefit from oxygen therapy during activity even if they do not meet the criteria for LTOT. The demonstration of a positive response to oxygen therapy (ie, improved exercise endurance and reduced dyspnea) is required, and careful follow-up is mandatory (level of evidence: 3B).

Ambulatory oxygen

In patients with resting hypoxemia, LTOT provided by a stationary system may limit their ability to remain active by encouraging psychological dependence and fear of leaving home. Combined domiciliary and ambulatory oxygen has been proposed as a solution for this problem (163,164). Although portable oxygen delivery systems are currently available, they are expensive and no study has firmly demonstrated their effectiveness in improving patient-orientated clinical outcomes. Ambulatory oxygen might increase compliance with oxygen by increasing the daily dose (165). It might also increase mobility, exercise tolerance, confidence and autonomy (166), although the potential for a placebo effect is very high. Therefore, careful patient selection, formal assessments and subsequent supervision are recommended (167).

INTEGRATED MANAGEMENT OF SEVERE COPD

There is currently no cure for COPD, but by following combined therapeutic modalities patients can reasonably expect to breathe more easily, to be more active, to have fewer acute exacerbations and to spend less time in hospital. It is important to emphasize that combined therapies may have additive or synergistic effects. Thus, bronchodilators improve ventilatory capacity, which, when combined with exercise training, allows patients to further increase their exercise capacity. The combined modalities can result in a myriad of small physiological changes (rarely measured) in the cardiorespiratory systems and peripheral muscles, which culminate in meaningful improvements in the individual's health status (Figure 8).

AECOPD

Acute exacerbations are the most frequent cause of medical visits, hospital admissions and death among patients with COPD (168). In addition, frequent exacerbations are an important determinant of quality of life measures in this group of patients (169) and contribute to accelerated rates of decline in lung function (170). One of the limiting factors in discussing recommendations for the treatment of AECOPD is the lack of a clear definition of the term (171). ***The Panel proposed that AECOPD be defined as a sustained worsening of dyspnea, cough or sputum production leading to an increase in the use of maintenance medications and/or supplementation with additional medications (level of evidence: 3).*** The term 'sustained' is added to separate an AECOPD from the normal day-to-day variations in COPD symptoms. Although not strictly defined because some patients may have sudden and dramatic worsening of symptoms, it implies a change from baseline lasting 48 hours or more. In addition, exacerbations should be defined as either purulent or nonpurulent because this is helpful in predicting the need for antibiotic therapy (level of evidence: 2A).

The average COPD patient experiences two to three exacerbations per year. The frequency of exacerbations is, at least in part, related to the severity of underlying air flow obstruction: patients with a lower FEV_1 have more frequent exacerbations. Patients with mild to moderate disease have a 4% short term mortality if admitted to hospital (170,172), but mortality rates can be as high as 24% if patients are admitted to an intensive care unit (ICU) with respiratory failure (173-176). In addition, this group of patients requiring ICU admission has a one-year mortality rate as high as 46%. A significant percentage of patients requiring hospitalization for AECOPD require subsequent readmissions because of persistent symptoms and experience at least a temporary decrease in their functional abilities following discharge (173,177,178).

At least one-half of AECOPD are thought to be infectious in nature. Many of these are viral in origin and the remainder are due to bacterial infection. Other triggering factors for exacerbations include congestive heart failure, exposure to allergens and irritants (ie, cigarette smoke, dust, cold air or pollutants).

Diagnostic evaluation

A complete history and physical examination should be performed to rule out other causes for worsening cough and dyspnea. Most laboratory testing is discouraged, with the possible exception of arterial blood gases in a subset of patients who have low arterial oxygen saturations on oximetry. Chest x-rays are recommended for patients presenting to the emergency department or for admission to hospital because they have been shown to reveal abnormalities that lead to a change in management in 16% to 21% of patients (179,180) (level of evidence: 2).

For patients presenting with purulent sputum, the role for sputum Gram stain and culture remains undefined. The Panel suggested that sputum Gram stain and culture should be considered for patients with very poor lung function, frequent exacerbations or those who have been on antibiotics in the preceding three months (level of evidence: 3).

It is not recommended that spirometry be performed during the actual exacerbation, except perhaps for diagnostic purposes in patients with chronic symptoms without a known history of COPD (level of evidence: 3). Pulmonary function tests should be performed in patients suspected of having COPD following recovery if they have not previously had spirometry (level of evidence: 3).

Management of exacerbations

Bronchodilators: Inhaled bronchodilators should be used to treat dyspnea in AECOPD (level of evidence: 2A). Although most studies do not reveal any additional benefit from combining an inhaled short-acting beta$_2$-agonist with an inhaled anticholinergic drug, there are some patients who clearly benefit from combination therapy (181-184). Therefore, combination therapy is still recommended in the acute situation (level of evidence: 3). There is no difference in the objective outcomes between the use of nebulized bronchodilators or bronchodilators given through an MDI with a spacer (185-189). Due to the lower cost of using MDIs with a spacer, this route is preferred in most situations (level of evidence: 1B). There is no role for the initiation of therapy with methylxanthines during an AECOPD (level of evidence: 1E). For patients who are already on an oral methylxanthine product, it is reasonable to continue the medication during an AECOPD (level of evidence: 3C). However, in this circumstance, one must consider the possibility of drug interactions with antibiotics and monitor the dose accordingly.

Corticosteroid therapy: There is good evidence to support the use of oral or parenteral steroids for 14 days in most moderate to severe patients with AECOPD (level of evidence: 1A) (190-194). The exact dose and duration of therapy should be individualized, but treatment periods of between seven and 14 days seem reasonable (level of evidence: 3). Dosages of 25 mg to 50 mg of prednisone equivalent per day are suggested (level of evidence: 3). The role for oral steroid therapy in outpatients with milder disease (FEV_1 greater than 60% predicted) remains unclear. Similarly, the role of high dose ICS therapy during an AECOPD warrants further investigation before specific recommendations can be made.

Antibiotics: Several randomized, placebo-controlled trials of antibiotic therapy have been performed in AECOPD (195-203). Based on the results of these studies, it is recognized that antibiotics are beneficial in the treatment of more severe AECOPD (level of evidence: 1A). Anthonisen et al (195) have shown that patients with more severe exacerbations are likely to experience greater benefit from antibiotics (level of evidence: 1B).

Recommendation

- The Panel proposes that antibiotics should only be considered for use in patients with purulent exacerbations.

Patients should then be divided into two groups, simple or complicated exacerbations, based on the presence of risk factors that either increase the likelihood of treatment failure or are more likely to be associated with more virulent or resistant microbial pathogens (Table 11). Patients with simple AECOPD have no risk factors for treatment failure, and antibiotic therapy should be targeted against the most likely pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*). Although antibiotic therapy has been found to be beneficial in hastening recovery and preventing deterioration in this group of patients, no benefit of one group of antibiotics over another has been demonstrated. Many of these studies were performed before concerns regarding increasing antibiotic resistance were common. Nonetheless, in the absence of reports of clinical failures caused by antibiotic resistance in this group, relatively inexpensive antibiotics are still recommended (level of evidence: 3).

Patients with complicated AECOPD have risk factors that have been associated with an increased likelihood of treatment failure and/or infection with more virulent or resistant organisms. As a result, antibiotics with enhanced antimicrobial coverage are recommended. Fluoroquinolones have been shown to have enhanced eradication of potentially pathogenic bacteria compared with extended spectrum macrolides (204-207) or aminopenicillins and cephalosporins (207). They may lead to longer infection-free intervals, suggesting they may be a better choice for the treatment of infections in COPD patients with multiple risk factors or frequent exacerbations (206). An alternative choice is an amoxicillin-clavulinic acid combination. It is recommended that if a patient requires repeated antibiotic therapy within a three-month period, a different class of antibiotics should be used to avoid the increased risk of developing resistance.

NONINVASIVE MECHANICAL VENTILATION

Numerous randomized controlled trials and a recent systematic review support the benefit of noninvasive positive pressure ventilation (NPPV) in the setting of acute exacerbations (208-219). NPPV should be strongly considered in AECOPD with associated respiratory failure indicated by persistent respiratory acidosis despite initial therapy with bronchodilators (pH less than 7.3) (level of evidence: 1A). There is also a strong suggestion that the use of noninvasive ventilation in this setting is cost effective (220) (level of evidence: 2A).

Not all patients with COPD exacerbations benefit from NPPV (Table 12). The lower the pH (especially when the pH is less than 7.25) and higher the partial pressure of arterial carbon dioxide ($PaCO_2$) at presentation, the less likely patients are to respond (213). Patients treated with NPPV who do not

TABLE 11
Antibiotic treatment recommendations for purulent acute exacerbations of chronic obstructive pulmonary disease (COPD)

Group failure	Basic clinical state	Symptoms and risk factors	Probable pathogens	First choice	Alternatives for treatment
Simple	COPD without risk factors	Increased cough and sputum, sputum purulence, and increased dyspnea	*Haemophilus influenzae*, *Haemophilus* species, *Moraxella catarrhalis*, *Streptococcus pneumoniae*	Amoxicillin, doxycycline, trimethoprim/sulfamethoxazole, second- or third-generation cephalosporins, extended spectrum macrolides	Beta-lactam/beta-lactamase inhibitor; fluoroquinolone
Complicated	COPD with risk factors	As in simple plus (at least one of): FEV_1<50% predicted ≥ four exacerbations/year Ischemic heart disease Use of home oxygen Chronic oral steroid use Antibiotic use in the past three months	As in simple plus *Klebsiella* species and other Gram-negatives Increased probability of beta-lactam resistance	Beta-lactam/beta-lactamase inhibitor; fluoroquinolone (Antibiotics for uncomplicated patients when combined with oral steroids may suffice)	May require parenteral therapy Consider referral to a specialist or hospital

FEV_1 Forced expiratory volume in 1 s

TABLE 12
Patient selection for noninvasive ventilation

Criteria suggesting benefit	Criteria suggesting lack of benefit	Contraindications
Respiratory distress:	Milder exacerbations:	Respiratory arrest
Respiratory rate >25	pH >7.35	Hemodynamic instability
User of accessory muscles	Mild respiratory distress	Recent facial or gastroesophageal surgery
Respiratory acidosis:	Very severe exacerbations:	Craniofacial trauma
pH <7.35	pH <7.20	Fixed nasopharyngeal abnormalities
$PaCO_2$ >45 mmHg	Somnolence	Coma
	Lack of response to NPPV:	
	Increase or no change in respiratory rate	
	Decrease or no change in pH	
	Excessive secretions	

NPPV Noninvasive positive pressure ventilation; $PaCO_2$ Partial pressure of arterial carbon dioxide

improve within the first four hours are unlikely to benefit from NPPV (221,222). These patients should be closely monitored because they have a higher likelihood of requiring conventional mechanical ventilation (level of evidence: 2B). Conversely, patients with normal or mildly reduced pH (greater than 7.3) who are not in respiratory extremis also do not seem to clearly benefit from the addition of NPPV (223) (level of evidence: 1B).

A large randomized controlled trial on the use of NPPV in patients with AECOPD treated on a respiratory ward rather than the ICU reported a reduction in mortality for the group treated with NPPV for both those with severe (pH less than 7.3) or less severe exacerbations (219). However, the mortality rate of the severe subgroup of patients treated on the ward with NPPV was higher than that reported in the literature for apparently similar patients treated in the ICU. As such, in patients with severe COPD exacerbations, NPPV should be initiated in a setting that provides adequate cardiopulmonary monitoring (level of evidence: 2B).

A recent systematic review of the literature (four small trials) (224) concluded that the use of NPPV in hypercapnic patients with stable COPD (ie, patients who are not currently exacerbating) has not demonstrated any consistent clinically or statistically significant impact on outcome and, therefore, cannot be recommended at this time.

Recommendations

- NPPV should be considered in patients presenting with a severe exacerbation of COPD (pH less than 7.3).
- Patients with milder exacerbations do not benefit from NPPV.
- NPPV should be administered in a setting that allows close cardiopulmonary monitoring.
- NPPV is not indicated for patients who have had a respiratory arrest, who have hemodynamic instability, who are at high risk for aspiration, who have impaired mental status or who are otherwise unable to cooperate.
- There is no evidence to date that supports the use of NPPV for stable COPD patients with chronic hypercapnia.

TABLE 13
Summary of outcomes from randomized controlled trials for lung volume reduction surgery

Author, year (reference)	FEV_1	FVC	RV	TLC	ABG (mmHg)	Exercise	QoL	Survival
Criner et al, 1999 (231)	+10%*	+12%*	–66%*	–21%*	PaO_2: NS; PCO_2: -4*	6MWD: NS	Sickness impact profile: 10 vs 21*	9.4% mortality post op
Geddes et al, 2000 (234)	+0.10 L (NS)	NS	–62%*	–1% (NS)	PaO_2: NS; PCO_2: NS	Shuttle test: NS	SF-36: 43 vs 72*	21% vs 12% (NS)
Pompeo et al, 2000 (235)	+0.45 L*	–	–1.4 L*	–	PaO_2: +3*; PCO_2: NS	6MWD: 93 m vs 31 m*	–	6.7% vs 13.3%

**Statistically significant difference detected between LVRS group and control group. Results of Criner et al (1999) are reported three months post LVRS, Geddes et al (2000) are reported one year post LVRS, and Pompeo et al (2000) are at variables times post LVRS. 6MWD 6-minute walk distance; ABG Arterial blood gases; FEV_1 Forced expiratory volume in 1 s; FVC Forced vital capacity; NS No statistically significant difference detected between LVRS group and control group; $PaCO_2$ Partial pressure of arterial carbon dioxide; PaO_2 Partial pressure of arterial oxygen; Post op Post operative; QoL Quality of life; RV Residual volume; TLC Total lung capacity*

TABLE 14
Selection criteria for lung volume reduction surgery

Indications	Contraindications
Disability from emphysema (not from bronchitis or asthma) despite maximal medical treatment	Comorbid disease (ie, operation prohibitive risk or life expectancy less than two years)
	Severe obesity or cachexia
Age less than 75 to 80 years·	Severe coronary artery disease
Abstinence from smoking more than four months	Active smoker
FEV_1 <40% predicted	Alpha-1 antitrypsin deficiency
TLC >120% predicted	Extensive pleural symphysis
RV >175% predicted	Chest wall deformity
Hyperinflation, preferably with upper lobe dominance by computed tomography scan (heterogeneous distribution)	$PaCO_2$ >50 to 60 mmHg
	PAP >35 mmHg (mean)
	$FEV_1 \leq 20\%$ predicted and homogeneous distribution or DLCO <20% predicted

DLCO Diffusing capacity from carbon monoxide; FEV_1 Forced expiratory volume in 1 s; $PaCO_2$ Partial pressure of arterial carbon dioxide; PAP Pulmonary arterial pressure; RV Residual volume; TLC Total lung capacity

SURGERY

LVRS

LVRS removes 20% to 35% of the most emphysematous lung in COPD patients. The surgery was introduced by Brantigan et al (225) in the late 1950s as a way of palliating patients with emphysema. Cooper et al (226) reintroduced the operation in 1994. In carefully selected patients, improved outcomes have been demonstrated using the stapling-excision technique and the median sternotomy approach (227) (level of evidence: 2B). These improvements appear to be sustained for at least three years (228). Bilateral LVRS has better results than unilateral LVRS (229) (level of evidence: 2B). Resection of lung tissue produces better results than laser ablations (230) (level of evidence: 1B).

To date, there have been five randomized clinical trials, two from the United States (231,232) and one each from Sweden (233), the United Kingdom (234) and Italy (235), all of which report better outcomes in the surgical arms three to 12 months after surgery (Table 13). These trials did not include large numbers of patients (n=37 to 60 patients) and we await the results of larger trials with longer duration follow-up: the National Emphysema Treatment Trial (NETT), the Overholt Blue-Cross Emphysema Surgery Trial (OBEST) and the Canadian Lung Volume Reduction Trial (CLVRT). The NETT has already established a subgroup of patients with emphysema who do not benefit from LVRS (236) (level of evidence: 1E). These are patients with an FEV_1 of less than 20% predicted, and either homogeneous distribution emphysema or a diffusing capacity of no more than 20% predicted. Determination of the long term benefits from LVRS in terms of quality of life years awaits the results of longer, ongoing randomized controlled trials (Table 14).

The Panel believes there is significant heterogeneity in the existing published randomized controlled trials in terms of outcome measures and duration of follow-up. All have small numbers and significant methodological flaws. Therefore, any definitive recommendations on LVRS await the results of current prospective multicentre trials. In the interim, the Panel can offer general guidelines only (Table 14).

Lung transplantation for COPD

Lung transplantation is an excellent option for certain carefully selected patients with advanced COPD (level of evidence: 3A). Over 12,000 lung transplants have been performed to date, with COPD accounting for 60% and 30% of the single and bilateral procedures, respectively (237). Anticipated survival rates following lung transplantation for all disease states are in the range of 75% at one year and 50% at five years (237). However, recipients with COPD appear to have better outcomes than those with other conditions (level

of evidence: 3B). Chronic graft dysfunction associated with obliterative bronchiolitis, thought to be a manifestation of chronic rejection, is the major complication affecting long term morbidity and mortality, and is present in at least one-half of long term survivors (238).

In contrast to patients with cystic fibrosis or pulmonary fibrosis, the survival advantage with lung transplantation has not clearly been demonstrated for all patients with COPD (239,240) (level of evidence: 3C). Unfortunately, prospective studies examining which patients are most likely to benefit are lacking. Recent international guidelines for the selection of COPD patients who may be appropriate for lung transplantation emphasize the need for optimization of medical therapy (including pulmonary rehabilitation), as well as consideration of LVRS in appropriate individuals (241).

The Panel believes that preference should be given to those patients with elevated $PaCO_2$ with progressive deterioration who require LTOT because they have the poorest prognosis (level of evidence: 3B).

Lung transplant recipients can achieve substantial improvements in exercise capacity (242) (level of evidence: 2A), and the great majority of patients are free of supplemental oxygen. Data available to date indicate that these patients also attain important improvements in health-related quality of life (243) (level of evidence: 2A). More than 80% of lung transplant recipients surviving longer than five years report no activity limitation, and almost one-half of lung transplant recipients in the United States are working five years following the procedure (237).

At present, the number of potential lung transplant recipients far outstrips the donor supply, a reality that will continue to limit the widespread use of lung transplantation for the treatment of advanced respiratory disease (244). The Panel believes that validated selection criteria need to be developed to help determine which COPD patients derive the greatest benefit from lung transplantation.

Recommendation

- Patients with COPD are considered to be potentially in the transplant window if they meet at least one of the following criteria: FEV_1 less than 25% predicted (without reversibility), $PaCO_2$ greater than 55 mmHg or elevated pulmonary artery pressures with progressive deterioration (eg, cor pulmonale) (level of evidence: 3B).

ALPHA$_1$ ANTITRYPSIN DEFICIENCY

The CTS has published detailed guidelines on the assessment and management of alpha$_1$ antitrypsin (AAT) deficiency (245). Only pertinent summary information is provided here.

It was recommended that any patient with atypical features of COPD, including patients with early-onset disease, a positive family history, or those who become disabled in their 40s or 50s, be screened for AAT deficiency and AAT phenotype (Pi type). All provincial health plans should cover the cost of this screening. The Panel strongly recommends participation in the Alpha$_1$ Canadian Registry (<www.alpha1canadianregistry.com>, telephone 1-800-352-8186), which was established in 1999 under the auspices of the CTS in collaboration with the Alpha One International Registry.

There are currently three studies that have evaluated the effects of AAT replacement therapy: two nonrandomized studies comparing patients on replacement therapy with those not receiving AAT (246,247) and a small randomized trial of monthly AAT replacement (248). Taking these studies in aggregate, the subcommittee concluded that replacement therapy remained an unproven treatment, but there was some evidence suggesting a possible benefit to patients with an FEV_1 35% to 65% predicted.

Recommendation

- The Panel recommends restricting the option for AAT replacement therapy to AAT-deficient patients with an FEV_1 greater than 35% and less than 50% predicted who have quit smoking and are on optimal medical therapy yet continue to show a rapid decline in FEV_1 (greater than 80 mL/year).

END-OF-LIFE ISSUES IN COPD

In 1998, COPD accounted for over 5000 deaths, or 4% of all deaths in Canada. Mortality during admission with an exacerbation of COPD ranges from 10% to 20%. Age, presence of gas-exchange abnormalities, low body mass index score and poor functional status are important predictors of death (249-253). Unfortunately, it remains difficult to accurately predict short term survival of individual hospitalized COPD patients. Survival from acute respiratory failure complicating an exacerbation of COPD is high (75% to 90%), especially with the use of noninvasive ventilation in carefully selected patients and settings (249-253).

The quality of life of patients with advanced COPD is often poor. There is considerable discordance between the informaton that patients wish and expect to receive regarding their disease and its prognosis and what their physicians provide. The Panel believes that we need to improve our understanding of patients' experiences and needs through well-timed, honest, informative and emphatic, yet realistic, conversations that can form the basis of effective advanced care planning. Discussions about end-of-life issues often occur too late, are held in inappropriate settings (such as the ICU) and do not meet the expectations of patients (253). Lack of access to formal palliative care services or pulmonary rehabilitation programs means that family physicians and respirologists provide the bulk of end-of-life care to COPD patients. The Panel believes that patients with advanced disease who have survived an ICU admission for respiratory failure should particularly be targeted for effective end-of-life care during follow-up outpatient visits.

Symptom control

It is reasonable to optimize and maximize bronchodilator therapy in dyspneic patients in the final phases of their illness. The role of oxygen in the palliation of dyspnea in mildly hypoxic, advanced COPD has not been adequately investigated. Without further study, the routine use of oxygen for dyspnea palliation in COPD patients without severe hypoxia cannot be justified.

Opioids reduce ventilation in COPD patients in response to a variety of stimuli, including exercise and blood gas abnormalities (254). Clinically, respiratory depression is an uncommon problem if patients are initiated on a low dose and titrated slowly (255). As well, tolerance to the respiratory depressant effects develop quickly. The risk of respiratory depressant effects of opioids increases with dose, rate of administration, prior opioid use, combined use with any other respiratory depressants and advanced age (256,257) (Table 15).

The emotional consequences of severe COPD include anxiety, fear, panic and depression. These psychological factors can impose an additional barrier to effective symptom control (6,258), further reduce quality of life and require pharmacological and nonpharmacological treatment strategies for effective management (219).

Noninvasive ventilation may be effective (with likely reversible causes of acute respiratory failure) and may also provide some symptom relief in COPD patients who otherwise would not accept intubation and mechanical ventilation (219). However, further studies are required to establish this.

Recommendations

- COPD patients should be encouraged to articulate to their physicians and caregivers a desire for information about their disease, prognosis and the possible circumstances of their death (level of evidence: 2A).
- All physicians who care for COPD patients should possess the necessary skills to conduct discussions with their patients about end-of-life issues. This will likely require changes to current medical school curricula and continuing medical education programs to better equip future and currently practicing clinicians, respectively (level of evidence: 2A).
- Family physicians and respirologists require further education to help them identify which COPD patients in their practice are at an increased risk of dying in the near future and who would, therefore, benefit most from timely discussions about end-of-life issues (level of evidence: 2A).
- Physicians require increased education about how to incorporate pharmacological and nonpharmacological treatments to achieve optimal symptom control in severe COPD

Health policy issues

A better process to formulize access to palliative care services for clinicians providing care for COPD patients is required (level of evidence: 3B). For patients admitted to hospital, we should consider whether changes to institutional policies and procedures (eg, use of admission standing orders) would help to identify hospitalized patients at risk of dying and to systematically ensure that discussions regarding end-of-life care take place between clinicians and hospitalized COPD patients.

FUTURE THERAPIES IN COPD

A number of novel therapies have been developed to suppress the inflammatory process in the hope of modifying disease progression in COPD (259-261). Experimental therapies include inflammatory mediator antagonists such as leukotriene B_4 inhibitors, tumor necrosis factor-alpha inhibitors, chemokine inhibitors, antioxidants and prostanoid inhibitors. Other anti-inflammatory therapies in development include phosphodiesterase type 4 inhibitors, interleukin-10, mitogen-activated protein kinase inhibitors and adhesion molecule blockers. New antineutrophil therapies under investigation include prostaglandin E2 and colchicine.

Metalloproteinases are released from inflammatory cells in the lung in COPD and are thought to play an important role in its pathogenesis. Protease inhibitors and metalloproteinase inhibitors may favourably modify the inflammatory response and prevent progression.

New mucoregulators, which reduce mucous hypersecretion and improve mucociliary clearance, also have the potential to improve airway dysfunction in COPD. Finally, animal studies have recently shown that retinoic acid may reverse proteolytic destruction and help stimulate growth of damaged alveoli.

Phosphodiesterase type 4 inhibitors

Phosphodiesterase type 4 inhibitors are currently being clinically evaluated in COPD. They combine anti-inflammatory and bronchodilator effects and have been shown in prelimi-

TABLE 15
Agents used to manage symptoms related to chronic obstructive pulmonary disease at the end of life

Indication	Drug	Commonly used dosage
Dyspnea	Morphine	
	Oral	5-10 mg q4 h
	Per rectum	5-10 mg q4 h
	IV, SQ or IM	Titrate to relieve dyspnea
	Nebulized	5 mg in 2 mL normal saline q4 h with hand-held nebulizer
	Benzodiazepines	
	Lorazepam, oral, sublingual, IV	1-2 mg q1-4 h
	Diazepam, oral, IV	2.5-25 mg daily
	Midazolam, SQ	5-10 mg SQ, then 10-30 mg continuous SQ infusion for two days
	Other	
	Chlorpromazine, IV	12.5 mg IV q4-6 h
	Chlorpromazine, per rectum	25 mg q4-6 h
Cough	Opioids	
	Codeine, oral	30-60 mg q4 h
	Morphine, IV	2.5-5 mg q4 h
	Inhaled anesthetics	
	Bupivacaine, 0.25%	5 mg q4-6 h
Retained secretions	Anticholinergic agents	
	Scopolamine, SQ	0.4 to 0.6 mg q4-6 h
	Scopolamine, transdermal patch	1.5 mg q72 h
	Hyoscyamine, SQ	0.25-0.5 mg q4-6 h
	Atropine, SQ	0.4 mg q4-6 h

IM Intramuscular; IV Intravenous; q Every; SQ Subcutaneous

nary studies to improve lung function to a level comparable to that of existing bronchodilators (262-264). No information is available as to whether these drugs (eg, cilomilast, roflumilast) delay the rate of progression of the disease.

FUTURE RESEARCH QUESTIONS AND SUGGESTIONS

Screening

- Does targeted screening of symptomatic smokers or exsmokers improve overall outcomes in COPD?
- Is the brief COPD test suggested by the Panel (see Clinical Assessment section) valid and useful in clinical practice?
- Does spirometry augment smoking cessation interventions?

Disease stratification and differential diagnosis

- Is the proposed stratification system, based on the MRC scale, of clinical utility?
- There is a need to develop and test stratification systems that incorporate measures of impairment, disability and handicap.
- There is a need to develop better criteria to distinguish COPD from asthma, both clinically and in the laboratory (eg, biomarkers).

Disease subgroups

- Is it possible to identify discrete disease subgroups in COPD by clinical and laboratory measures?
- Do such subgroups vary in their response to therapeutic interventions and in their natural history?

Natural history of COPD

- There is a need to conduct large population-based studies to delineate the natural history of COPD using a variety of relevant parameters, both clinical and biological.

Assessment

- Does a more comprehensive assessment of COPD patients lead to better clinical outcomes?

Management

- What type of educational programs work best for COPD patients and what outcomes best evaluate this?

Pharmacotherapy

- Are the effects of combined long-acting bronchodilators (anticholinergics and LABAs) superior to each agent alone in terms of mechanics, exercise capacity, exacerbation reduction and improved quality of life?
- Does the addition of ICS to patients maximally bronchodilated with long-acting anticholinergics and beta$_2$-agonists convey additional improvements in mechanics, dyspnea, exercise tolerance, exacerbations and quality of life?
- What criteria should be used to define clinical responses to ICS and systemic steroids?
- What should be the sequence of introduction of bronchodilators and inhaled steroids in a given patient?
- What is the effect of inhaled steroids on inflammatory markers in COPD in the long term?

Acute exacerbations

- What is the pathophysiology of AECOPD?
- What are the relative roles of steroids and antibiotics?
- There is a need to compare the effects of first-line and second-line antibiotics in the treatment of purulent exacerbations of less severe COPD.
- What are the factors that predict a poor outcome during AECOPD?
- What are the criteria to identify patients with exacerbations requiring hospitalization?
- In a nonpurulent exacerbation, what is the effect of steroids in patients with different levels of disease severity?
- What is the role of ICS and oral steroids in mild, simple AECOPD?
- Is there a role for high dose ICS in AECOPD?
- What is the role of action plans in the management of AECOPD? Are they effective?

Pulmonary rehabilitation

- There is a need to study the effects of strength and endurance training on both the short term and long term outcomes of COPD.
- What is the role of community-based programs in maintaining the results of short exercise training programs?
- What is the cost effectiveness of rehabilitation programs when added to smoking cessation programs?
- There is a need to study the effects of various interventions (eg, nutrition, anabolic steroids, growth hormone analog) on peripheral muscle function and exercise capacity in COPD.
- There is a need to study the effects of chronic hypoxia on peripheral muscle function in COPD.
- There is a need to better understand cardiopulmonary interactions during exercise in COPD.

Oxygen

- What is the role of oxygen therapy in patients who only desaturate during exercise?
- What exercise test best identifies an oxygen responder?
- What is the role of ambulatory oxygen as an adjunct to exercise training in COPD?
- What is the role of oxygen therapy on the long term outcomes of patients who demonstrate isolated nocturnal desaturation?
- What is the impact of combined COPD and sleep apnea on morbidity and mortality in COPD?
- What is the efficacy of noninvasive ventilatory support in patients with coexistent obstructive sleep apnea and COPD?

Clinical trial outcomes

- What are the clinically significant changes in the TDI and in various health status questionnaires following therapeutic interventions in COPD?

End-of-life research

- Studies are required to determine the definitive role of opioid therapy, supplemental oxygen therapy and noninvasive ventilatory assistance on the symptoms and quality of life in patients with end-stage COPD.
- What are the caregiver and economic burdens for end-of-life care of the COPD population in Canada?

Sponsoring Organizations: Canadian College of Family Physicians, The Lung Association, Canadian Nurses' Respiratory Society, Canadian Physiotherapy Cardio-Respiratory Society, Respiratory Therapy Society of The Lung Association, and the Canadian COPD Alliance.

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