NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PART I. DIAGNOSIS AND MANAGEMENT OF STABLE COPD

Guidelines

1. **Finnish Medical Society Duodecim**. Chronic obstructive pulmonary disease (COPD). In: EBM Guidelines. Evidence-Based Medicine. Helsinki, Finland: Duodecim Medical Publications Ltd.; 2007 Feb 7 [various].
2. **Global Initiative for Chronic Obstructive Lung Disease (GOLD)**. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization, National Heart, Lung and Blood Institute; 2007. [420 references]
3. **National Collaborating Centre for Chronic Conditions, National Institute for Health and Clinical Excellence (NCCCC/NICE)**. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004 Feb;59 Suppl 1:1-232. [491 references]
4. **Singapore Ministry of Health**. Chronic obstructive pulmonary disease. Singapore: Singapore Ministry of Health; 2006 Oct. 84 p. [155 references]

INTRODUCTION

A direct comparison of the Finnish Medical Society Duodecim (FMS), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (a collaborative project of the World Health Organization and the National Heart, Lung, and Blood Institute), the National Collaborating Centre for Chronic Conditions (a collaborating center for the National Institute for Health and Clinical Excellence [NCCCC/NICE]), and the Singapore Ministry of Health (SMOH) recommendations for the diagnosis and management of stable COPD is provided in the tables below.

All four guidelines are broad in scope, providing recommendations on diagnosis and management of both stable COPD and acute exacerbations of disease. The GOLD guideline also addresses prevention strategies; the GOLD, NCCCC/NICE and SMOH guidelines address pulmonary rehabilitation. These topics, however, are beyond the scope of this synthesis. NCCCC/NICE also provides recommendations for drug delivery systems (including inhalers, spacers, and nebulizers) and the management of pulmonary hypertension and cor pulmonale. Recommendations for the diagnosis and management of acute exacerbations of COPD are compared in Part II of this synthesis. Recommendations for pulmonary rehabilitation of patients with COPD are addressed in Part III of this synthesis.

The FMS and GOLD guidelines are updates of previous versions. In developing their guidelines both GOLD and SMOH reviewed the 2004 NCCCC/NICE guideline; SMOH also reviewed the 2005 version of the GOLD guideline.

The tables below provide a side-by-side comparison of key attributes of each guideline, including specific interventions and practices that are addressed. The language used in these tables, particularly that which is used in Table 3, Table 4, Table 5 is in most cases taken verbatim from the original guidelines:

- Table 1 provides a quick-view glance at the primary interventions considered by each group and which make up the focus of this guideline synthesis.
- Table 2 provides a comparison of the overall scope of the included guidelines.
- Table 3 provides a more detailed comparison of the specific recommendations offered by each group for the topics under consideration in this synthesis, including:
    - Diagnosis and Initial Assessment
        - Definition of COPD
        - Symptoms/Medical History
        - Physical Examination
        - Measurement of Airflow Limitation--Spirometry
        - Differential Diagnosis
        - Bronchodilator Reversibility Testing
        - Chest X-Ray
        - Measurement of Arterial Blood Gases/Oximetry
        - Measurement of Alpha-1 Antitrypsin (AAT) Levels
        - Additional Investigations
        - Assessing Severity of Disease
    - Overall Management Strategy
    - Pharmacologic Interventions
        - General Approach to Pharmacologic Therapy
        - Bronchodilators
        - Corticosteroids
        - Combination Therapy
        - Vaccines
        - Alpha-1 Antitrypsin Augmentation Therapy
        - Antibiotics
        - Mucolytic Therapy
        - Antioxidant Agents
        - Antitussives
    - Non-Pharmacologic Interventions
        - Long-term Oxygen Therapy (LTOT)
        - Lifestyle Modification
        - Patient Education
        - Surgery
    - Ongoing Assessment and Follow-Up
- Table 4 lists the potential benefits and harms associated with the implementation of each guideline as stated in the original guidelines.
- Table 5 presents the rating schemes used by the guideline groups to rate the level of evidence and the strength of the recommendations.

A summary discussion of the areas of agreement and areas of differences among the guidelines is presented following the content comparison tables.

Related Guidelines

- Institute for Clinical Systems Improvement (ICSI). Chronic obstructive pulmonary disease. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2007 Jan. 65 p. [125 references]
- American Medical Directors Association (AMDA). COPD management in the long-term care setting. Columbia (MD): American Medical Directors Association (AMDA); 2003. 32 p. [15 references]

Abbreviations used in the text and tables:

- AAT, Alpha1-antitrypsin
- BMI, Body mass index
- CT, Computed tomography
- COPD, Chronic obstructive pulmonary disease
- ERS, European Respiratory Society
- FMS, Finnish Medical Society Duodecim
- FEV_1, Forced expiratory volume in one second
- FVC, Forced vital capacity
- GOLD, Global Initiative for Chronic Obstructive Lung Disease
- HRCT, High-resolution computed tomography
- LABA, long-acting $beta_2$-agonist
- LTOT, Long-term oxygen therapy
- LVRS, Lung volume reduction surgery
- MRC, Medical Research Council
- NCCCC, National Collaborating Centre for Chronic Conditions
- NICE, National Institute for Health and Clinical Excellence
- PEF, Peak expiratory flow
- PEP, Positive expiratory pressure
- SAAC, short-acting anti-cholinergic
- SABA, short-acting $beta_2$-agonist
- SMOH, Singapore Ministry of Health
- T_LCO, Transfer factor for carbon monoxide
- VC, Vital capacity

TABLE 1: COMPARISON OF INTERVENTIONS AND PRACTICES CONSIDERED
("✓" indicates topic is addressed)

	FMS (2007)	GOLD (2007)	NCCCC/NICE (2004)	SMOH (2006)
Diagnosis and Initial Assessment	✓	✓	✓	✓
Overall Management Strategy	✓	✓	✓	✓
Pharmacologic	✓	✓	✓	✓

Interventions				
Non-Pharmacologic Interventions	✓	✓	✓	✓
Ongoing Assessment and Follow-Up		✓	✓	✓

TABLE 2: COMPARISON OF SCOPE AND CONTENT	
Objective and Scope	
FMS (2007)	• Evidence-Based Medicine Guidelines collect, summarize, and update the core clinical knowledge essential in general practice. The guidelines also describe the scientific evidence underlying the given recommendations.
GOLD (2007)	• To increase awareness of COPD and decrease morbidity and mortality from the disease • To improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy • To encourage an expanded level of research interest in this highly prevalent disease • To work toward combating the nihilistic attitude toward COPD by disseminating information about available treatments (both pharmacologic and nonpharmacologic) and by working with a network of experts—the Global Initiative for Chronic Obstructive Lung Disease (GOLD) National Leaders—to implement effective COPD management programs developed in accordance with local health care practices
NCCCC/NICE (2004)	• To develop a clinical guideline on the management of chronic obstructive pulmonary disease for use in the National Health Service (NHS) in England and Wales • To offer best practice advice on the identification and care of patients with COPD • To define the symptoms, signs, and investigations required to establish a diagnosis of COPD • To define the factors that are necessary to assess the severity of COPD, provide prognostic information, and guide best management • To provide guidance on the pharmacological and non-pharmacological treatment of patients with stable COPD and

	on the management of exacerbations • To discuss the interface with surgery and intensive therapy units
SMOH (2006)	• To give physicians a practical approach and guide to the care of COPD patients
Target Population	
FMS (2007)	• Finland • Adults with COPD • Adults requiring evaluation for possible chronic obstructive pulmonary disease
GOLD (2007)	• Individuals with COPD
NCCCC/NICE (2004)	• England and Wales • Adults who have a clinical working diagnosis of COPD, including chronic bronchitis, emphysema, and chronic airflow limitation/obstruction **Note**: The guideline does not cover the management of people with asthma, bronchopulmonary dysplasia, and bronchiectasis, nor does it cover children.
SMOH (2006)	• Singapore • Patients with known or suspected COPD
Intended Users	
FMS (2007)	Health Care Providers Physicians
GOLD (2007)	Advanced Practice Nurses Allied Health Personnel Nurses Physician Assistants Physicians

	Public Health Departments Respiratory Care Practitioners
NCCCC/NICE (2004)	Advanced Practice Nurses Allied Health Personnel Dietitians Health Care Providers Hospitals Nurses Occupational Therapists Patients Physical Therapists Physicians Public Health Departments Respiratory Care Practitioners Students
SMOH (2006)	Physicians

TABLE 3: COMPARISON OF RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF STABLE COPD	
DIAGNOSIS AND INITIAL ASSESSMENT	
Definition of COPD	
FMS (2007)	**COPD**: the patient has chronic, progressive airway obstruction, with poor response to treatment. Other typical findings include chronic bronchitis and emphysema in varying grades depending on the patient.

GOLD (2007)	COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.
NCCCC/NICE (2004)	COPD is characterized by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking. • Airflow obstruction is defined as a reduced FEV_1 and a reduced FEV_1/FVC ratio, such that FEV_1 is less than 80% predicted and FEV_1/FVC is less than 0.7. • The airflow obstruction is due to a combination of airway and parenchymal damage. • The damage is the result of chronic inflammation that differs from that seen in asthma and which is usually the result of tobacco smoke. • Significant airflow obstruction may be present before the individual is aware of it. • COPD produces symptoms, disability, and impaired quality of life which may respond to pharmacological and other therapies that have limited or no impact on the airflow obstruction. • COPD is now the preferred term for the conditions in patients with airflow obstruction who were previously diagnosed as having chronic bronchitis or emphysema. • Other factors, particularly occupational exposures, may also contribute to the development of COPD. There is no single diagnostic test for COPD. Making a diagnosis relies on clinical judgement based on a combination of history, physical examination and confirmation of the presence of airflow obstruction using spirometry.
SMOH (2006)	**Definition** COPD is a heterogeneous disorder characterised by airflow obstruction that is not fully reversible. The airflow limitation is usually both progressive and associated with exposure to noxious particles or gases.
Symptoms/Medical History	
FMS (2007)	**Symptoms** • Cough and sputum excretion are the most common

	symptoms. • Patients with progressive disease suffer from slowly increasing dyspnoea during exercise. • The symptoms are aggravated by respiratory infection.

GOLD (2007)	**Key Points**:
	
	• A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease (see below). The diagnosis should be confirmed by spirometry.
	
	Key Indicators for Considering a Diagnosis of COPD
	
	Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.
	
	• **Dyspnea that is**:
	  • Progressive (worsens over time)
	  • Persistent (present every day)
	  • Described by the patient as: "increased effort to breathe," "heaviness," "air hunger," or "gasping"
	  • Worse on exercise
	  • Worse during respiratory infections
	• **Chronic cough**: Present intermittently or every day. Often present throughout the day; seldom only nocturnal
	• **Chronic sputum production**: Any pattern of chronic sputum production may indicate COPD
	• **History of exposure to risk factors**, especially:
	  • Tobacco smoke
	  • Occupational dusts and chemicals
	  • Smoke from home cooking and heating fuels
	
	Note: Refer to the original guideline document for additional discussion of the above symptoms.
	
	Medical History
	
	A detailed medical history of a new patient known or thought to have COPD should assess:
	
	• Exposure to risk factors
	• Past medical history, including asthma, allergy, sinusitis or nasal polyps, respiratory infections in childhood, and

	other respiratory diseases • Family history of COPD or other chronic respiratory disease • Pattern of symptom development • History of exacerbations or previous hospitalizations for respiratory disorder • Presence of comorbidities, such as heart disease, malignancies, osteoporosis, and musculoskeletal disorders, which may also contribute to restriction of activity • Appropriateness of current medical treatments • Impact of disease on patient's life, including limitation of activity; missed work and economic impact; effect on family routines; and feelings of depression or anxiety • Social and family support available to the patient • Possibilities for reducing risk factors, especially smoking cessation
NCCCC/NICE (2004)	The diagnosis of COPD depends on thinking of it as a cause of breathlessness or cough. The diagnosis is suspected on the basis of symptoms and signs and supported by spirometry. **Symptoms** **D** - A diagnosis of COPD should be considered in patients over the age of 35 who have a risk factor (generally smoking) and who present with one or more of the following symptoms: • Exertional breathlessness • Chronic cough • Regular sputum production • Frequent winter "bronchitis" • Wheeze **D** - Patients in whom a diagnosis of COPD is considered should also be asked about the presence of the following factors: • Weight loss • Effort intolerance • Waking at night • Ankle swelling • Fatigue • Occupational hazards • Chest pain • Haemoptysis **Note**: These last two symptoms are uncommon in COPD and raise the possibility of an alternative diagnosis. **D** - One of the primary symptoms of COPD is breathlessness.

	The Medical Research Council (MRC) dyspnoea scale (for an adaptation of the scale, see Table 3 in the original guideline document) should be used to grade the breathlessness according to the level of exertion required to elicit it.
SMOH (2006)	**Clinical Assessment** **D** - A diagnosis of COPD should be considered in any patient more than 35 years old, who has chronic cough, sputum production, or dyspnoea, and/or a history of exposure to risk factors for the disease (see Table 4 in the original guideline document). **(Grade D, Level 4)**
Physical Examination	

FMS (2007)	• Most patients seek a doctor late, when the disease is already moderate to severe. In mild disease auscultation may be normal and no auscultatory signs for obstruction can be detected.
	• The following symptoms indicate severe COPD; their absence does not exclude the existence of mild COPD:
	  • Because of airway obstruction, wheezing rattles may be heard at the end of forced expiration.
	  • The patient with advanced emphysema may have a barrel-chested appearance, on auscultation silent respiratory sounds are heard, and on percussion the sound is hypersonor.
	  • Cyanosis is associated with hypoxaemia.

GOLD (2007)	Though an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are usually not present until significant impairment of lung function has occurred, and their detection has a relatively low sensitivity and specificity. A number of physical signs may be present in COPD, but their absence does not exclude the diagnosis. *Inspection* • Central cyanosis, or bluish discoloration of the mucosal membranes, may be present but is difficult to detect in artificial light and in many racial groups. • Common chest wall abnormalities, which reflect the pulmonary hyperinflation seen in COPD, include relatively horizontal ribs, "barrel-shaped" chest, and protruding abdomen. • Flattening of the hemi-diaphragms may be associated with paradoxical in-drawing of the lower rib cage on inspiration, reduced cardiac dullness, and widening

	xiphisternal angle. • Resting respiratory rate is often increased to more than 20 breaths per minute and breathing can be relatively shallow. • Patients commonly show pursed-lip breathing, which may serve to slow expiratory flow and permit more efficient lung emptying. • COPD patients often have resting muscle activation while lying supine. Use of the scalene and sternocleidomastoid muscles is a further indicator of respiratory distress. • Ankle or lower leg edema can be a sign of right heart failure. *Palpation and Percussion* • These are often unhelpful in COPD. • Detection of the heart apex beat may be difficult due to pulmonary hyperinflation. • Hyperinflation also leads to downward displacement of the liver and an increase in the ability to palpate this organ without it being enlarged. *Auscultation* • Patients with COPD often have reduced breath sounds, but this finding is not sufficiently characteristic to make the diagnosis. • The presence of wheezing during quiet breathing is a useful pointer to airflow limitation. However, wheezing heard only after forced expiration is of no diagnostic value. • Inspiratory crackles occur in some COPD patients but are of little help diagnostically. • Heart sounds are best heard over the xiphoid area.
NCCCC/NICE (2004)	No recommendations offered.
SMOH (2006)	**Physical Examination** Physical examination is rarely diagnostic in COPD. Physical signs of airflow obstruction, e.g., hyperinflation, are rarely present until significant lung function impairment has occurred. Hence their detection has a low sensitivity and specificity. Physical signs of airflow obstruction that that may be present are:

	• Hyperinflated chest • Purse lip breathing • Use of accessory muscle • Paradoxical movements of lower ribs • Reduced crico-sternal distance • Reduced cardiac dullness • Wheeze or quiet breath sounds Loss of muscle mass and peripheral muscle weakness are present in advanced disease.
Measurement of Airflow Limitation--Spirometry	
FMS (2007)	Early diagnosis by spirometry combined with active promotion of smoking cessation is pursued. According to the international criteria, the threshold value for the diagnosis of mild COPD is FEV_1/FVC <70% after the bronchodilating test, when FEV% is >80%.
GOLD (2007)	**Key Points**: • For the diagnosis and assessment of COPD, spirometry is the gold standard as it is the most reproducible, standardized, and objective way of measuring airflow limitation. The presence of a postbronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted confirms the presence of airflow limitation that is not fully reversible. • Health care workers involved in the diagnosis and management of COPD patients should have access to spirometry. **Measurement of Airflow Limitation (Spirometry)** Spirometry should be undertaken in all patients who may have COPD. It is needed to make a confident diagnosis of COPD and to exclude other diagnoses that may present with similar symptoms. Although spirometry does not fully capture the impact of COPD on a patient's health, it remains the gold standard for diagnosing the disease and monitoring its progression. It is the best standardized, most reproducible, and most objective measurement of airflow limitation available. Good quality spirometric measurement is possible and all health care workers who care for COPD patients should have access to spirometry. Figure 5.1-4 in the original guideline document summarizes some of the factors needed to achieve accurate test results. Spirometry should measure the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity,

	FVC) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. Spirometry measurements are evaluated by comparison with reference values based on age, height, sex, and race.
NCCCC/NICE (2004)	**D** - Spirometry should be performed: • At the time of diagnosis • To reconsider the diagnosis if patients show an exceptionally good response to treatment **D** - All health professionals managing patients with COPD should have access to spirometry and be competent in the interpretation of the results. **D** - Spirometry can be performed by any healthcare worker who has undergone appropriate training and who keeps his or her skills up to date. **D** - Spirometry services should be supported by quality control processes. **D** - It is recommended that European Respiratory Society (ERS) 1993 reference values* are used but it is recognised that these values may lead to under-diagnosis in the elderly and are not applicable in black and Asian populations. *Quanjer PH, Tammeling GJ, Cotes JE et al. (1993) Lung volumes and forced ventilator flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* (Suppl) 16:5-40. **Identification of Early Disease** **D** - Spirometry should be performed in patients who are over 35, current or ex-smokers, and have a chronic cough. **B** - Spirometry should be considered in patients with chronic bronchitis. A significant proportion of these will go on to develop airflow limitation.
SMOH (2006)	**Lung Function Tests** **Spirometry** **D** - Spirometry is useful for the definitive diagnosis of COPD

	and for the staging of disease severity, and should be performed in individuals with symptoms suggestive of COPD. **(Grade D, Level 4)** Spirometry should measure the maximal volume of air forcibly exhaled from the point of maximal inhalation (forced vital capacity, FVC) and the volume of air exhaled during the first second of this maneuvre (forced expiratory volume in one second, FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. The primary benefit of spirometry is to identify COPD patients who may benefit from pharmacologic treatment in order to improve symptoms and exacerbations. Spirometry for case finding among all adults with a history of exposure to pulmonary risk factors, whether they have persistent respiratory symptoms or not, is unlikely to be beneficial unless future studies establish that spirometry improves smoking cessation rate, or that treatments other than smoking cessation benefit individuals with airflow obstruction who do not report respiratory symptoms. Spirometry for monitoring individuals or adjusting treatment is unlikely to be beneficial unless future studies establish that relative effectiveness between therapies varies according to an individual's baseline or follow-up spirometry.
Differential Diagnosis	
FMS (2007)	Most important differential diagnostic problem is asthma. Also many asthmatics smoke.
GOLD (2007)	**Differential Diagnosis** In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques and it is assumed that asthma and COPD coexist in these patients. In these cases, current management is similar to that of asthma. Other potential diagnoses are usually easier to distinguish from COPD (see below). **Differential Diagnosis of COPD** COPD • Onset in mid-life • Symptoms slowly progressive • Long history of tobacco smoking • Dyspnea during exercise

- Largely irreversible airflow limitation

Asthma

- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms at night/early morning
- Allergy, rhinitis, and/or eczema also present
- Family history of asthma
- Largely reversible airflow limitation

Congestive Heart Failure

- Fine basilar crackles on auscultation
- Chest x-ray shows dilated heart, pulmonary edema.
- Pulmonary function tests indicate volume restriction, not airflow limitation

Bronchiectasis

- Large volumes of purulent sputum
- Commonly associated with bacterial infection
- Coarse crackles/clubbing on auscultation
- Chest x-ray/computed tomography shows bronchial dilation, bronchial wall thickening.

Tuberculosis

- Onset all ages
- Chest x-ray shows lung infiltrate
- Microbiological confirmation
- High local prevalence of tuberculosis

Obliterative Bronchiolitis

- Onset in younger age, nonsmokers
- May have history of rheumatoid arthritis or fume exposure
- Computed tomography on expiration shows hypodense areas.

Diffuse Panbronchiolitis

- Most patients are male and nonsmokers.
- Almost all have chronic sinusitis
- Chest x-ray and high resolution computed tomography (HRCT) show diffuse small centrilobular nodular opacities and hyperinflation.

Note: *These features tend to be characteristic of the respective diseases, but do not occur in every case. For*

	example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even elderly patients.

NCCCC/NICE (2004)	**D** - COPD and asthma are frequently distinguishable on the basis of history (and examination) in untreated patients presenting for the first time. Features from the history and examination should be used to differentiate COPD from asthma whenever possible.
	
	Clinical features differentiating COPD and asthma include:
	
	• Smoker or ex-smoker:
	  • COPD: nearly all
	  • Asthma: possibly
	• Symptoms under age 35:
	  • COPD: rare
	  • Asthma: common
	  • Chronic productive cough:
	  • COPD: common
	  • Asthma: uncommon
	  • Breathlessness:
	  • COPD: persistent and progressive
	  • Asthma: variable
	  • Night time waking with breathlessness and/or wheeze:
	  • COPD: uncommon
	  • Asthma: common
	  • Significant diurnal or day to day variability of symptoms:
	  • COPD: uncommon
	  • Asthma: common
	
	D - Longitudinal observation of patients (whether using spirometry, peak flow, or symptoms) should also be used to help differentiate COPD from asthma.

SMOH (2006)	**Differential Diagnosis** A major differential diagnosis of COPD is bronchial asthma. These two conditions are frequently distinguishable on the basis of history and examination in untreated patients presenting for the first time. Table 1 in the original guideline document shows the features that help to differentiate between COPD and Asthma. **D** - Where diagnostic doubt remains, or both COPD and asthma are present, the following findings will help identify

	asthma: • A large response (FEV_1 greater than 400 mL) to bronchodilators. • A large response (FEV_1 greater than 400 mL) to 30 mg oral prednisolone daily for 2 weeks. • Serial peak flow measurements showing 20% or greater diurnal or day-to-day variability. **(Grade D, Level 4)** The definition of COPD requires confirmation of persistent airflow obstruction after administration of a bronchodilator. Bronchoreversibility, however, cannot serve as an absolute criterion for separating asthma from COPD. On the other hand, documentation of complete reversibility is useful in excluding COPD, and a documentation of bronchoreversibility of a rise of FEV_1 >400 mL has been suggested to indicate such a reversibility. Similarly, a variation of 20% or greater diurnal or day-to-day variability is the level for documenting complete bronchoreversibility. **D** - Where chronic asthma cannot be distinguished from COPD with the current imaging or lung function testing, it is assumed that the two diseases co-exist and their management should be similar to that of asthma. **(Grade D, Level 4)** **D** - COPD should be differentiated from congestive heart failure, bronchiectasis, and obliterative bronchiolitis. **(Grade D, Level 4)** Congestive heart failure, bronchiectasis, and obliterative bronchiolitis may present with similar symptoms and signs as COPD. These conditions may mimic COPD or may co-exist in a patient with COPD. See Table 2 in the original guideline document.
Bronchodilator Reversibility Testing	
FMS (2007)	Test with a bronchodilating drug • The response to a bronchodilating drug is measured either by spirometry that is combined with a dose of a broncholytic drug (e.g., inhaled salbutamol 400 micrograms) or by PEF-measurements performed before and after the administration of the drug. In COPD, there is no response (cf. asthma).

GOLD (2007)	**Additional Investigations** For patients diagnosed with *Stage II: Moderate COPD* and beyond, the following additional investigations may be considered: ***Bronchodilator reversibility testing.*** Despite earlier hopes, neither bronchodilator nor oral glucocorticosteroid reversibility testing predicts disease progression, whether judged by decline in FEV_1, deterioration of health status, or frequency of exacerbations in patients with a clinical diagnosis of COPD and abnormal spirometry. Small changes in FEV_1 (e.g., < 400 mL) after administration of a bronchodilator do not reliably predict the patient's response to treatment (e.g., change in exercise capacity). Minor variations in initial airway caliber can lead to different classification of reversibility status depending on the day of testing, and the lower the pre-bronchodilator FEV_1, the greater the chance of a patient being classified as reversible even when the 200 mL volume criterion is included. In some cases (e.g., a patient with an atypical history such as asthma in childhood and regular night waking with cough or wheeze) a clinician may wish to perform a bronchodilator and/or glucocorticosteroid reversibility test and a possible protocol is suggested below. **Bronchodilator Reversibility Testing in COPD** <u>Preparation</u> • Tests should be performed when patients are clinically stable and free from respiratory infection. • Patients should not have taken inhaled short-acting bronchodilators in the previous six hours, long-acting $beta_2$-agonists in the previous 12 hours, or sustained-release theophylline in the previous 24 hours. <u>Spirometry</u> • FEV_1 should be measured before a bronchodilator is given. • The bronchodilator should be given by metered dose inhaler through a spacer device or by nebulizer to be certain it has been inhaled. • The bronchodilator dose should be selected to be high on the dose/response curve. • Possible dosage protocols are 400 micrograms $beta_2$-agonist, up to 160 micrograms anticholinergic, or the two combined. FEV_1 should be measured again 10 to 15 minutes after a short-acting bronchodilator is given; 30 to

	45 minutes after the combination. Results • An increase in FEV_1 that is both greater than 200 mL and 12% above the pre-bronchodilator FEV_1 is considered significant. It is usually helpful to report the absolute change as well as the % change from baseline to set the improvement in a clinical context.
NCCCC/NICE (2004)	**D** - In most patients, routine spirometric reversibility testing is not necessary as a part of the diagnostic process or to plan initial therapy with bronchodilators or corticosteroids. It may be unhelpful or misleading because: • **B** - Repeated FEV_1 measurements can show small spontaneous fluctuations. • **B** - The results of a reversibility test performed on different occasions can be inconsistent and not reproducible. • **B** - Over-reliance on a single reversibility test may be misleading unless the change in FEV_1 is greater than 400 mL. • **B** - The definition of the magnitude of a significant change is purely arbitrary. • **A** - Response to long-term therapy is not predicted by acute reversibility testing. **D** - To help resolve cases where diagnostic doubt remains, or both COPD and asthma are present, the following findings should be used to help identify asthma: • A large (greater than 400 mL) response to bronchodilators • A large (greater than 400 mL) response to 30 mg oral prednisolone daily for 2 weeks • Serial peak flow measurements showing 20% or greater diurnal or day-to-day variability Clinically significant COPD is not present if the FEV_1 and FEV_1/ FVC ratio return to normal with drug therapy. **D** - If patients report a marked improvement in symptoms in response to inhaled therapy, the diagnosis of COPD should be reconsidered.
SMOH (2006)	**Evaluation** **D** - It is also recommended that bronchodilator reversibility

	testing be performed to help identify some subjects with asthma or a large asthma component to COPD and to establish a patient's best attainable lung function **(Grade D, Level 4)**
Chest X-ray	
FMS (2007)	Chest x-ray is of limited value in COPD diagnosis.
GOLD (2007)	**Additional Investigations** For patients diagnosed with *Stage II: Moderate COPD* and beyond, the following additional investigations may be considered: **Chest X-ray**. An abnormal chest x-ray is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities such as cardiac failure. Radiological changes associated with COPD include signs of hyperinflation (flattened diaphragm on the lateral chest film, and an increase in the volume of the retrosternal air space), hyperlucency of the lungs, and rapid tapering of the vascular markings. CT of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, HRCT scanning might help in the differential diagnosis. In addition, if a surgical procedure such as lung volume reduction is contemplated, a chest CT scan is necessary since the distribution of emphysema is one of the most important determinants of surgical suitability.
NCCCC/NICE (2004)	**D** - At the time of their initial diagnostic evaluation, in addition to spirometry all patients should have a chest radiograph to exclude other pathologies
SMOH (2006)	**Evaluation** **D** - A chest X-ray is seldom diagnostic in COPD but it is valuable in excluding alternative diagnoses and should be performed to look for abnormalities that may suggest other conditions. Computed tomography of the chest is not routinely recommended. **(Grade D, Level 4)**
Measurement of Arterial Blood Gases/Oximetry	
FMS (2007)	Blood gas analysis • In late stages of COPD arterial blood oxygen partial pressure (pO_2) decreases and carbon dioxide partial

	pressure (pCO_2) may increase.
GOLD (2007)	**Additional Investigations** For patients diagnosed with *Stage II: Moderate COPD* and beyond, the following additional investigations may be considered: ***Arterial blood gas measurement.*** In advanced COPD, measurement of arterial blood gases while the patient is breathing air is important. This test should be performed in stable patients with FEV_1 < 50% predicted or with clinical signs suggestive of respiratory failure or right heart failure. Several considerations are important to ensure accurate test results. The inspired oxygen concentration (FiO_2 — normally 21% at sea level) should be noted, a particularly important point if patient is using an O_2-driven nebulizer. Changes in arterial blood gas tensions take time to occur, especially in severe disease. Thus, 20 to 30 minutes should pass before rechecking the gas tensions when the FiO_2 has been changed (e.g., during an assessment for domiciliary oxygen therapy). Adequate pressure must be applied at the arterial puncture site for at least one minute, as failure to do so can lead to painful bruising.
NCCCC/NICE (2004)	**D** - Additional investigations should be performed to aid management in some circumstances, including: • **Pulse oximetry** - To assess need for oxygen therapy; if cyanosis or cor pulmonale present, or if FEV_1
SMOH (2006)	**Evaluation** **D** - Arterial blood gases should be performed in patients with FEV_1 <40% predicted or with clinical signs suggestive of respiratory failure or right heart failure. **(Grade D, Level 4)**
Measurement of Alpha-1 Antitrypsin (AAT) Levels	
FMS (2007)	Deficiency of alpha-1 antitrypsin is noted as a rare cause of emphysema in young patients.
GOLD (2007)	**Additional Investigations** For patients diagnosed with *Stage II: Moderate COPD* and beyond, the following additional investigations may be

	considered: ***Alpha-1 antitrypsin deficiency screening.*** In patients of Caucasian descent who develop COPD at a young age (<45 years) or who have a strong family history of the disease, it may be valuable to identify coexisting AAT deficiency. This could lead to family screening or appropriate counseling. A serum concentration of AAT below 15 to 20% of the normal value is highly suggestive of homozygous AAT deficiency.
NCCCC/NICE (2004)	**D** - Additional investigations should be performed to aid management in some circumstances, including: • **Alpha-1 antitrypsin** - if early onset, minimal smoking history or family history **D** - Patients identified as having alpha-1 antitrypsin deficiency should be offered the opportunity to be referred to a specialist centre to discuss the clinical management of this condition.
SMOH (2006)	No recommendations offered.
Additional Investigations	

FMS (2007)	• The effectiveness of anti-inflammatory treatment is evaluated with a trial of steroids.
	  • Oral prednisolone, initially 30 to 40 mg/day (if necessary, give protection against ulcers, e.g., a proton pump inhibitor), or inhaled steroid (e.g., budesonide 400 to 800 micrograms twice daily). In oral administration the duration of the trial is 2 weeks, with an inhaled steroid 6 weeks.
	  • An objective response (PEF increase >20% and/or FEV_1 increase >12% and at least 200 mL) is indicative of asthma.
	• Diffusion capacity
	  • Decreased in COPD

GOLD (2007)	CT of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, HRCT scanning might help in the differential diagnosis. In addition, if a surgical procedure such as lung volume reduction is contemplated, a chest CT scan is necessary since the distribution of emphysema is one of the most important determinants of surgical suitability.
NCCCC/NICE (2004)	**D** - At the time of their initial diagnostic evaluation, in addition

	to spirometry and chest radiograph all patients should have: • A full blood count to identify anaemia or polycythaemia • BMI calculated **D** - Additional investigations should be performed to aid management in some circumstances (see Additional Investigations below). **Additional Investigations**: • **Serial domiciliary peak flow instruments** - To exclude asthma if diagnostic doubt remains • **Transfer factor for carbon monoxide (T_LCO)** - To investigate symptoms that seem disproportionate to the spirometric impairment • **Computed tomography (CT) scan of the thorax** - To investigate symptoms that seem disproportionate to the spirometric impairment; to investigate abnormalities seen on a chest radiograph; to assess suitability for surgery • **Electrocardiogram (ECG)** - To assess cardiac status if features of cor pulmonale • **Echocardiogram** - To assess cardiac status if features of cor pulmonale • **Sputum culture** - To identify organisms if sputum is persistently present and purulent
SMOH (2006)	No recommendations offered.
Assessing Severity of Disease	
FMS (2007)	Mild disease: • Asymptomatic patients • Patients with occasional symptoms (generally FEV_1 >50% predicted) Continuous symptoms (FEV_1 generally <50% predicted)
GOLD (2007)	**Assessment of COPD Severity** Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality (Figure 1-2 in the original guideline document), and the presence of complications such as respiratory failure, right heart failure, weight loss, and arterial hypoxemia.

	Spirometric Classification of Severity For educational reasons, a simple spirometric classification of disease severity into four stages is recommended (see below). Spirometry is essential for diagnosis and provides a useful description of the severity of pathological changes in COPD. Specific spirometric cut-points (e.g., post-bronchodilator FEV_1/FVC ratio < 0.70 or FEV_1 < 80, 50, or 30% predicted) are used for purposes of simplicity: these cut-points have not been clinically validated. **Stage I [Mild COPD]:** • FEV_1/FVC < 0.70 • $FEV_1 \geq$80% predicted **Stage II [Moderate COPD]:** • FEV_1/FVC < 0.70 • 50% $\leq FEV_1$ <80% predicted **Stage III [Severe COPD]:** • FEV_1/FVC < 0.70 • 30% $\leq FEV_1$ <50% predicted **Stage IV [Very Severe COPD]:** • FEV_1/FVC < 0.70 • FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure
NCCCC/NICE (2004)	COPD is heterogeneous, so no single measure can give an adequate assessment of the true severity of the disease in an individual patient. Severity assessment is, nevertheless, important because it has implications for therapy and relates to prognosis. **D** - Mild airflow obstruction can be associated with significant disability in patients with COPD. A true assessment of severity should include assessment of the degree of airflow obstruction and disability, the frequency of exacerbations and the following known prognostic factors: • FEV_1 • T_LCO • Breathlessness (MRC scale) • Health status

	• Exercise capacity • BMI • Partial pressure of oxygen in arterial blood (PaO_2) • Cor pulmonale. **D** - The severity of airflow obstruction should be assessed according to the reduction in FEV_1 as follows: • Mild airflow obstruction: 50 to 80% predicted FEV_1 • Moderate airflow obstruction: 30 to 49% predicted FEV_1 • Severe airflow obstruction: <30% predicted FEV_1
SMOH (2006)	**Classification of Severity** **Spirometry** **D** - A classification of disease severity into 5 stages based on spirometry cut points is recommended. **(Grade D, Level 4)** The FEV_1 and FEV_1/FVC cut-points used by the Global Initiative for Obstructive Lung Disease (GOLD) for classifying the severity of COPD into 5 stages is shown below. These cut points are used for the purposes of educational simplicity: they have not been clinically validated. Stage 0 [At Risk]: • Normal spirometry • Chronic symptoms (cough, sputum production) Stage I [Mild COPD]: • FEV_1/FVC <70% • $FEV_1 \geq$80% predicted • With or without chronic symptoms (cough, sputum production) Stage II [Moderate COPD]: • FEV_1/FVC <70% • 50%$\leq FEV_1$ <80% predicted • With or without chronic symptoms (cough, sputum production) Stage III [Moderate COPD]: • FEV_1/FVC <70% • 30%$\leq FEV_1$ <50% predicted

	• With or without chronic symptoms (cough, sputum production) Stage IV [Very Severe COPD] • FEV_1/FVC <70% FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure **Assessment of Severity** Assessment of severity is based on the patient's level of symptoms, the severity of the spirometric abnormality, and the presence of complications such as cor pulmonale, respiratory failure and right heart failure. Physical signs of cor pulmonale to look for are: • Central cyanosis • Raised jugular venous pressure • Left parasternal heave • Loud P2 and a loud ejection click • Pansystolic murmur or tricuspid regurgitation • Hepatomegaly • Peripheral oedema Progressive impairment of consciousness, the presence of a bounding pulse, flapping tremor and papilloedema indicate carbon dioxide retention and impending respiratory failure.
OVERALL MANAGEMENT STRATEGY	
FMS (2007)	No overall management strategy is provided. Basic rules for drug therapy, according to disease severity are provided (see below).
GOLD (2007)	An effective COPD management plan includes four components: (1) Assess and Monitor Disease; (2) Reduce Risk Factors; (3) Manage Stable COPD; and (4) Manage Exacerbations. Management of Mild to Moderate COPD (*Stages I and II*) involves the avoidance of risk factors to prevent disease progression and pharmacotherapy as needed to control symptoms. Severe (*Stage III*) and Very Severe (*Stage IV*) COPD often require the integration of several different disciplines, a variety of treatment approaches, and a commitment of the clinician to the continued support of the patient as the illness progresses. In addition to patient education, health advice, and pharmacotherapy, COPD patients may require specific counseling about smoking

	cessation, instruction in physical exercise, nutritional advice, and continued nursing support. Not all approaches are needed for every patient, and assessing the potential benefit of each approach at each stage of the illness is a crucial aspect of effective disease management. While disease prevention is the ultimate goal, once COPD has been diagnosed, effective management should be aimed at the following goals: • Relieve symptoms • Prevent disease progression • Improve exercise tolerance • Improve health status • Prevent and treat complications • Prevent and treat exacerbations • Reduce mortality
NCCCC/NICE (2004)	The management of an individual patient's disease should be guided by the symptoms and disability that they experience. At different times in the natural history of their disease different features may predominate, and their management will change to reflect this.
SMOH (2006)	No overall management strategy is provided.
PHARMACOLOGIC INTERVENTIONS	
General Approach to Pharmacologic Therapy	

FMS (2007)	**Basic Rules of Drug Therapy**
	
	Mild disease
	
	• Asymptomatic patients
	  • No drug therapy
	• Patients with occasional symptoms (generally FEV_1>50% predicted)
	  • Anticholinergics or short-acting $beta_2$-agonists according to clinical response
	  • Trial of steroids if asthma is suspected
	
	Continuous symptoms (FEV_1 generally)
	
	• Anticholinergics and short-acting $beta_2$-agonists (combined) according to clinical response
	• Long acting anticholinergic or $beta_2$-agonist, or their combination

	• In selected cases inhaled glucocorticoid if frequent exacerbations • Trial of theophylline if symptoms persist [**A**] • Surgery (bullectomy, lung transplantation, lung volume reduction) can be recommended only to a small subset of the patients after careful evaluation
GOLD (2007)	**Key Points**: • None of the existing medications for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease (**Evidence A**). Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications. **Overview of the Medications** Pharmacologic therapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease. However, this should not preclude efforts to use medications to control symptoms. Since COPD is usually progressive, recommendations for the pharmacological treatment of COPD reflect the following general principles: • Treatment tends to be cumulative with more medications being required as the disease state worsens. • Regular treatment needs to be maintained at the same level for long periods of time unless significant side effects occur or the disease worsens. • Individuals differ in their response to treatment and in the side effects they report during therapy. Careful monitoring is needed over an appropriate period to ensure that the specific aim of introducing a therapy has been met without an unacceptable cost to the patient. The effect of therapy in COPD may occur sooner after treatment with bronchodilators and inhaled glucocorticosteroids than previously thought, although at present, there is no effective way to predict whether or not treatment will reduce exacerbations.
NCCCC/NICE (2004)	**Key Priorities for Implementation** • Long-acting inhaled bronchodilators (beta$_2$-agonists and/or anticholinergics) should be used to control

	symptoms and improve exercise capacity in patients who continue to experience problems despite the use of short-acting drugs. • Inhaled corticosteroids should be added to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 less than or equal to 50% predicted who have had two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12-month period.
SMOH (2006)	**Goals of Pharmacotherapy in COPD** • Relieve, reduce and abolish symptoms • Increase exercise capacity • Reduce frequency and severity of acute exacerbations • Improve health related quality of life These goals should be achieved with minimum side-effects from the medications. There is currently no evidence that any pharmacotherapy influences lung function decline or mortality in COPD. Evidence from largescale studies regarding the effect of pharmacotherapy on these outcome measures is anticipated in the near future. **Principles of Therapy** • Treatment needs to be maintained long-term. • Treatment is according to stage of severity, with step-wise increase usually required, as COPD is a progressive disease. • Inhaled therapy via metered dose or dry powder inhalers is preferred. The use of a large-volume spacer is advised for patients who have difficulty mastering the metered-dose inhaler technique.
Bronchodilators	

FMS (2007)	• Inhaled short acting (ipratropium [**B**] or oxitropium bromide) or long acting (tiotropium [**A**]) anticholinergic drug
	  • First line treatment
	  • The dose must be high enough; administration 4 to 6 times daily with the short acting drug, once a day with the long acting tiotropium.
	• Inhaled beta-sympathomimetic (salbutamol, terbutaline, fenoterol) [**A**]

	• May be combined with an anticholinergic drug • Long-acting beta-sympathomimetics (formoterol, salmeterol [**B**]) may improve quality of life and reduce symptoms [**C**]. • Oral, long-acting theophylline [**A**] • Adverse effects (central nervous system, gastrointestinal symptoms) are common (follow-up of serum concentrations is necessary) • Arrhythmias and convulsions are signs of toxicity. • Keep in mind various interactions with other drugs (e.g., antibiotics)
GOLD (2007)	**Key Points**: • Bronchodilator medications are central to the symptomatic management of COPD (**Evidence A**). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations. • The principal bronchodilator treatments are $beta_2$-agonists, anticholinergics, and methylxanthines used singly or in combination (**Evidence A**). • Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (**Evidence A**). • The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV_1 < 50% predicted *(Stage III: Severe COPD and Stage IV: Very Severe COPD)* and repeated exacerbations (**Evidence A**). Bronchodilator medications are central to the symptomatic management of COPD (**Evidence A**) (see figure 5.3-5 in the original guideline document). They are given either on an as-needed basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. The side effects of bronchodilator therapy are pharmacologically predictable and dose dependent. Adverse effects are less likely, and resolve more rapidly after treatment withdrawal, with inhaled than with oral treatment. However, COPD patients tend to be older than asthma patients and more likely to have comorbidities, so their risk of developing side effects is greater. The classes of medications commonly used in treating COPD are shown in Figure 5.3-4 (below). The choice within each class depends on the availability of medication and the patient's response. **Commonly Used Formulations of Drugs used in COPD**

(from Figure 5-3.4 in the original guideline document. Refer to document for formulations).

Beta$_2$-agonists:

Short-acting

- Fenoterol
- Levalbuterol
- Salbutamol (albuterol)
- Terbutaline

Long-acting

- Formoterol
- Salmeterol

Anticholinergics:

Short-acting

- Ipratropium bromide
- Oxitropium bromide

Long-acting

- Tiotropium

Methylxanthines:

- Aminophylline (slow release preparations)
- Theophylline (slow release preparations)

All categories of bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV_1 (**Evidence A**). Regular treatment with long acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (**Evidence A**).

Regular use of a long-acting beta$_2$-agonist or long-acting anticholinergic improves health status. Treatment with a long-acting inhaled anti-cholinergic drug reduces the rate of COPD exacerbations and improves the effectiveness of pulmonary rehabilitation. Theophylline is effective in COPD, but due to its potential toxicity, inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.

	Note: Refer to the original guideline document for additional discussion of bronchodilator medications.
NCCCC/NICE (2004)	**Inhaled Bronchodilator Therapy** **B** - Short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation. **D** - The effectiveness of bronchodilator therapy should not be assessed by lung function alone but should include a variety of other measures such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief. **A** - Patients who remain symptomatic should have their inhaled treatment intensified to include long-acting bronchodilators or combined therapy with a short-acting beta$_2$-agonist and a short-acting anticholinergic. **A** - Long-acting bronchodilators should be used in patients who remain symptomatic despite treatment with short-acting bronchodilators, because these drugs appear to have additional benefits over combinations of short-acting drugs. **D** - Long-acting bronchodilators should also be used in patients who have two or more exacerbations per year. **D** - The choice of drug(s) should take into account the patient's response to a trial of the drug, the drug's side effects, patient preference, and cost. **Theophylline** In this section, the term theophylline is used to mean long-acting/slow-release formulations of this drug. **D** - Theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy, as there is a need to monitor plasma levels and interactions. **D** - Particular caution needs to be taken with the use of theophylline in elderly patients because of differences in pharmacokinetics, the increased likelihood of comorbidities, and the use of other medications. **D** - The effectiveness of the treatment with theophylline should be assessed by improvements in symptoms, activities

	of daily living, exercise capacity, and lung function. **D** - The dose of theophylline prescribed should be reduced at the time of an exacerbation if macrolide or fluoroquinolone antibiotics (or other drugs known to interact) are prescribed.
SMOH (2006)	**Pharmacotherapy for Stable COPD** **Short-acting Inhaled Bronchodilators** **A** - Inhaled short-acting bronchodilators are recommended as first-line therapy in all stages of COPD to relieve symptoms and improve exercise capacity. **(Grade A, Level 1+)** **Short-acting Beta$_2$-agonists (SABA)** Examples of inhaled short-acting beta$_2$-agonists: • Salbutamol (Ventolin®, Respolin®, Salamol®, Buventol®) • Terbutaline (Bricanyl®) • Fenoterol (Berotec®) Regular administration of inhaled short-acting beta$_2$-agonists is an effective and inexpensive treatment for the management of patients with stable COPD. SABAs produce bronchodilation more rapidly than anti-cholinergic agents, acting within 15 minutes of administration with effects lasting 4 to 5 hours. They may be used up to a maximum of 4 to 6 times a day. They may be used as on-demand medications for relief of acute dyspnoea and for prophylaxis prior to exertion. The main side-effects are tremor and palpitations. **Short-acting Anti-cholinergic (SAAC)** Example: ipratropium bromide (Atrovent®) Anti-cholinergic agents induce bronchodilation by attenuating vagal tone in the airways via the blockage of acetylcholine's effect on M3 receptors. Ipratropium bromide is either equivalent to or more potent than beta$_2$-agonist as a bronchodilator in COPD. It should be taken regularly (4 to 6 hourly) rather than on an as-needed basis because of its relatively slow onset of action. As quaternary anti-cholinergic agents are poorly absorbed into the circulation, they are virtually free of systemic side effects. The main side-effect is dryness of the mouth. Tachyphylaxis does not develop despite prolonged usage of anticholinergics.

Combination Inhaler Containing SAAC and SABA

Examples of combination products are:

- Fenoterol combined with ipratropium bromide (Berodual®, Duovent® nebuliser solution)
- Salbutamol combined with ipratropium bromide (Combivent®)

As beta$_2$-agonists and anticholinergics produce bronchodilation through different pathways, combination products were introduced in the hope of achieving greater bronchodilation than with monotherapy. The combination product was shown to produce greater and more sustained improvements in FEV_1 than either drug alone.

Long-acting Inhaled Bronchodilators

A - Regular treatment with one or both classes of the inhaled long-acting bronchodilators should be considered for patients with moderate to very severe COPD with frequent exacerbations. **(Grade A, Level 1+)**

D - Inhaled long-acting bronchodilators may be added to the treatment regimen when symptoms are not controlled with short-acting inhaled bronchodilators alone. **(Grade D, Level 4)**

Long-acting Beta$_2$-agonists (LABA)

Examples of long-acting inhaled 2-agonists:

- Salmeterol (Serevent®)
- Formoterol (Foradil®/ Oxis®)

Salmeterol and formoterol are potent beta$_2$-agonists with 12-hour or greater duration of action when inhaled by patients with partially reversible COPD.30 Formoterol has a faster onset of action (one to three minutes compared with 10 to 20 minutes for salmeterol). Peak effects are achieved at 1 to 2 hours for both compounds.

LABAs should be reserved for COPD patients who report definite improvement (in terms of better exercise capacity or reduced symptoms) whilst on this therapy.

Long-acting Anticholinergic

Tiotropium (Spiriva®) is the only long-acting cholinergic currently available. It has a duration of action greater than 24

	hours. Like ipratropium, tiotropium is poorly absorbed from the gastrointestinal tract and the lung, thus reducing systemic bioavailability and accounting for a favorable systemic safety profile. Tiotropium has been shown to be effective in reducing acute exacerbations, reducing symptoms and improving health-related quality of life compared to placebo and to ipratropium bromide. The effect of co-administration of other anticholinergic-containing drugs with tiotropium has not been studied and is best avoided. **Combined Use of a Short or Long-anticholinergic and LABA** Combining bronchodilators with different mechanisms and durations of actions may increase the degree of bronchodilation for equivalent or fewer side-effects. Previous studies in patients with moderate-to-severe stable COPD demonstrated that combination of ipratropium with either formoterol or salmeterol is more effective than a combination of the anti-cholinergic with SABAs, and shows additive effects in improving lung function. **Theophylline** **D** - Theophylline may be a useful addition where symptom control is still not achieved with existing inhaled bronchodilator therapy. Theophylline may be of value for patients who are non-adherent to or unable to use inhaled therapy. **(Grade D, Level 4)** Careful monitoring for side-effects and drug interactions is needed in view of its narrow therapeutic index. A target therapeutic range of 8 to 13 mg/dl is recommended. It is important to be aware of factors which decrease its clearance, including potential drug interactions, and which may precipitate drug toxicity (Table 6 in the original guideline document). Signs of toxicity include arrhythmias and convulsions.
Corticosteroids	
FMS (2007)	Inhaled steroids are prescribed for patients with frequent exacerbations [**B**].
GOLD (2007)	**Glucocorticosteroids**

The effects of oral and inhaled glucocorticosteroids in COPD are much less dramatic than in asthma, and their role in the management of stable COPD is limited to specific indications. The use of glucocorticosteroids for the treatment of acute exacerbations is described in *Component 4: Manage Exacerbations* of the original guideline document.

Oral glucocorticoids: short-term. Many existing COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticosteroids to identify COPD patients who might benefit from long-term treatment with oral or inhaled glucocorticosteroids.

There is mounting evidence, however, that a short course of oral glucocorticosteroids is a poor predictor of the long-term response to inhaled glucocorticosteroids in COPD. For this reason, there appears to be insufficient evidence to recommend a therapeutic trial with oral glucocorticosteroids in patients with *Stage II: Moderate COPD, Stage III: Severe COPD, or Stage IV:Very Severe COPD* and poor response to an inhaled bronchodilator.

Oral glucocorticoids: long-term. Based on the lack of evidence of benefit, and the large body of evidence on side effects, long-term treatment with oral glucocorticosteroids is not recommended in COPD **(Evidence A)**.

Inhaled glucocorticoids. Regular treatment with inhaled glucocorticosteroids does not modify the long-term decline of FEV_1 in patients with COPD. However, regular treatment with inhaled glucocorticosteroids is appropriate for symptomatic COPD patients with an FEV_1 <50% predicted *(Stage III: Severe COPD and Stage IV: Very Severe COPD)* and repeated exacerbations (for example, 3 in the last three years) (**Evidence A**). This treatment has been shown to reduce the frequency of exacerbations and thus improve health status (**Evidence A**), and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients.

An inhaled glucocorticosteroid combined with a long-acting $beta_2$-agonist is more effective than the individual components (**Evidence A**).

Glucocorticosteroid drugs used in treating COPD include:

<u>Inhaled Glucocorticosteroids</u>

- Beclomethasone
- Budesonide

	• Fluticasone • Triamcinolone <u>Systemic Glucocorticosteroids</u> • Prednisone • Methyl-prednisone
NCCCC/NICE (2004)	*Inhaled Corticosteroids* None of the inhaled corticosteroids currently available are licensed for use alone in the treatment of COPD. The following recommendations therefore include usage outside licensed indications, and prescribers need to remember that responsibility for such prescribing lies with them. **A** - Oral corticosteroid reversibility tests do not predict response to inhaled corticosteroid therapy and should not be used to identify which patients should be prescribed inhaled corticosteroids. **B** - Inhaled corticosteroids should be prescribed for patients with an FEV_1 less than or equal to 50% predicted, who are having two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12-month period. The aim of treatment is to reduce exacerbation rates and slow the decline in health status and not to improve lung function per se. **D** - Clinicians should be aware of the potential risk of developing osteoporosis and other side effects in patients treated with high-dose inhaled corticosteroids (especially in the presence of other risk factors), and should discuss the risk with patients. *Oral Corticosteroids* **D** - Maintenance use of oral corticosteroid therapy in COPD is not normally recommended. Some patients with advanced COPD may require maintenance oral corticosteroids when these cannot be withdrawn following an exacerbation. In these cases, the dose of oral corticosteroids should be kept as low as possible. **D** - Patients treated with long-term oral corticosteroid therapy should be monitored for the development of osteoporosis and given appropriate prophylaxis. Patients over the age of 65 should be started on prophylactic treatment, without monitoring.

SMOH (2006)	**A** - Inhaled corticosteroids as long-term maintenance therapy are recommended for patients with FEV_1 <50% predicted who experience frequent exacerbations. **(Grade A, Level 1+)** Examples of inhaled corticosteroids (ICSs) are beclomethasone dipropionate (Becloforte®), budesonide (Pulmicort®) and fluticasone propionate (Flixotide®). Unlike asthma where ICSs play a key anti-inflammatory role and are recommended first-line therapy, current evidence supports limiting the use of ICSs in COPD to patients with moderate to severe disease and who have frequent exacerbations. **Oral Corticosteroids** **A** - Long-term oral corticosteroids are not recommended in stable COPD. **(Grade A, Level 1+)** Although a short course of high dose oral corticosteroid (prednisolone 30 mg/day) can improve lung function in some COPD patients, long term use of lower doses (prednisolone at < 10 to 15 mg/day) does not prevent worsening of the condition and is associated with increased risk of adverse effects such as diabetes and osteoporosis.
Combination Therapy	
FMS (2007)	With continuous symptoms (FEV_1 generally <50% predicted) • Anticholinergics and short-acting $beta_2$-agonists (combined) according to clinical response or • Long acting anticholinergic or $beta_2$-agonist, or their combination
GOLD (2007)	***Combination bronchodilator therapy***. Combining bronchodilators with different mechanisms and durations of action might increase the degree of bronchodilation for equivalent or lesser side effects. For example, a combination of a short-acting $beta_2$-agonist and an anticholinergic produces greater and more sustained improvements in FEV_1 than either drug alone and does not produce evidence of tachyphylaxis over 90 days of treatment (**Evidence A**). The combination of a $beta_2$-agonist, an anticholinergic and/or theophylline may produce additional improvements in lung function and health status. Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one bronchodilator when side effects

	are not a limiting factor. Detailed assessments of this approach have not been carried out. ***Inhaled Glucocorticoids*** An inhaled glucocorticosteroid combined with a long-acting beta$_2$-agonist is more effective than the individual components (**Evidence A**). Combination drugs used in treating COPD include: <u>Combination Short-acting Beta$_2$-agonists Plus Anticholinergic in One Inhaler</u> • Fenoterol/Ipratropium • Salbutamol/Ipratropium <u>Combination Long-acting Beta$_2$-agonists Plus Glucocorticosteroids in One Inhaler</u> • Formoterol/Budesonide • Salmeterol/Fluticasone
NCCCC/NICE (2004)	**A** - If patients remain symptomatic on monotherapy, their treatment should be intensified by combining therapies from different drug classes. Effective combinations include: • Beta$_2$-agonist and anticholinergic • Beta$_2$-agonist and theophylline • Anticholinergic and theophylline • Long-acting beta$_2$-agonist and inhaled corticosteroids **D** - The clinical effectiveness of combined treatments can be assessed by improvements in symptoms, activities of daily living, exercise capacity, and lung function. Combination treatment should be discontinued if there is no benefit after 4 weeks.
SMOH (2006)	**Combination Inhaler Containing SAAC and SABA** Examples of combination products are: • Fenoterol combined with ipratropium bromide (Berodual®, Duovent® nebuliser solution) • Salbutamol combined with ipratropium bromide (Combivent®) As beta$_2$-agonists and anticholinergics produce bronchodilation

	through different pathways, combination products were introduced in the hope of achieving greater bronchodilation than with monotherapy. The combination product was shown to produce greater and more sustained improvements in FEV_1 than either drug alone. **Long-acting Inhaled Bronchodilators** **A** - Regular treatment with one or both classes of the inhaled long-acting bronchodilators should be considered for patients with moderate to very severe COPD with frequent exacerbations. **(Grade A, Level 1+)** **D** - Inhaled long-acting bronchodilators may be added to the treatment regimen when symptoms are not controlled with short-acting inhaled bronchodilators alone. **(Grade D, Level 4)** **Combined Use of a Short or Long-anticholinergic and LABA** Combining bronchodilators with different mechanisms and durations of actions may increase the degree of bronchodilation for equivalent or fewer side-effects. Previous studies in patients with moderate-to-severe stable COPD demonstrated that combination of ipratropium with either formoterol or salmeterol is more effective than a combination of the anti-cholinergic with SABAs, and shows additive effects in improving lung function. **Combination ICS + LABA** **D** - Combination inhaled corticosteroids and long-acting $beta_2$-agonists should be considered for patients in whom both its components are indicated. **(Grade D, Level 4)** The combination products available are Seretide® (fluticasone propionate + salmeterol xinafoate) and Symbicort® (budesonide + formoterol).
Vaccines	
FMS (2007)	• Influenza vaccination should be given yearly to all patients with clearly decreased ventilatory function [**C**]. • Pneumococcal vaccination may be beneficial [**C**].
GOLD (2007)	Influenza vaccines can reduce serious illness and death in COPD patients by about 50% (**Evidence A**). Vaccines containing killed or live, inactivated viruses are recommended

	as they are more effective in elderly patients with COPD. The strains are adjusted each year for appropriate effectiveness and should be given once each year. Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older. In addition, this vaccine has been shown to reduce the incidence of community-acquired pneumonia in COPD patients younger than age 65 with an FEV_1 < 40% predicted (**Evidence B**).
NCCCC/NICE (2004)	**HSC** - Pneumococcal vaccination and an annual influenza vaccination should be offered to all patients with COPD as recommended by the Chief Medical Officer. (**Evidence from Health Service Circulars [HSC]**) **NICE** - *"Within their licensed indications, zanamivir and oseltamivir are recommended for the treatment of at-risk adults who present with influenza-like illness and who can start therapy within 48 hours of the onset of symptoms."* (NICE technology appraisal guidance- No. 58. 2003) (**Evidence from NICE guidelines or Health Technology Appraisal Program**) The technology appraisal also notes that zanamivir should be used with caution in people with COPD because of risk of bronchospasm. If people with COPD are prescribed zanamivir, they should be made aware of the risks and have a fast-acting bronchodilator available.
SMOH (2006)	**C** - Annual influenza vaccination should be offered to the elderly (65 years and above) in all stages of COPD. **(Grade C, Level 2++)** **D** - Pneumococcal vaccination may be considered in COPD patients **(Grade D, Level 4)** **D** - If considering pneumococcal vaccination for a COPD patient, usually only one dose of the vaccine is needed. A second dose is recommended for persons aged 65 or older who received their first dose when they were under 65, if 5 or more years have passed since that dose. **(Grade D, Level 4)**
Alpha-1 Antitrypsin Augmentation Therapy	
FMS (2007)	No recommendations offered.
GOLD (2007)	Young patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy. However, this therapy is very expensive, is not available in most countries,

	and is not recommended for patients with COPD that is unrelated to alpha-1 antitrypsin deficiency (**Evidence C**).
NCCCC/NICE (2004)	**D** - Patients identified as having alpha-1 antitrypsin deficiency should be offered the opportunity to be referred to a specialist centre to discuss the clinical management of this condition. **D** - Alpha-1 antitrypsin replacement therapy is not recommended in the management of patients with alpha-1 antitrypsin deficiency
SMOH (2006)	No recommendations offered.
Antibiotics	
FMS (2007)	Antibiotics have no place in the basic maintenance therapy of COPD.
GOLD (2007)	***Antibiotics***. Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD and a study that examined the efficacy of winter chemoprophylaxis over a period of 5 years, concluded that there was no benefit. There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful (**Evidence A**).
NCCCC/NICE (2004)	**D** - There is insufficient evidence to recommend prophylactic antibiotic therapy in the management of stable COPD.
SMOH (2006)	**V. Others** There is no evidence to date to support the benefit of the routine use of maintenance antibiotic therapy, mucolytics/anti-oxidants respiratory stimulants, vasodilators, nedocromil sodium or leukotriene modifiers in stable COPD.
Mucolytic Therapy	
FMS (2007)	• If production of mucus is a problem, the patients is recommended to perform regular self-initiated mucus drainage sessions at home by exhaling air through a straw into a water-filled bottle, after, after which the expectorated mucus is coughed up [**D**]. • Mucolytic agents should be used only temporarily [**B**].
GOLD	***Mucolytic (mucokinetic, mucoregulator) Agents***:

(2007)	(ambroxol, erdosteine, carbocysteine, iodinated glycerol). The regular use of mucolytics in COPD has been evaluated in a number of long-term studies with controversial results. Although a few patients with viscous sputum may benefit from mucolytics, the overall benefits seem to be very small, and the widespread use of these agents cannot be recommended at present (**Evidence D**).
NCCCC/NICE (2004)	**B** - Mucolytic drug therapy should be considered in patients with a chronic cough productive of sputum. **D** - Mucolytic therapy should be continued if there is symptomatic improvement (for example, reduction in frequency of cough and sputum production).
SMOH (2006)	**V. Others** There is no evidence to date to support the benefit of the routine use of maintenance antibiotic therapy, mucolytics/anti-oxidants respiratory stimulants, vasodilators, nedocromil sodium or leukotriene modifiers in stable COPD.
Antioxidant Agents	
FMS (2007)	No recommendations offered.
GOLD (2007)	Antioxidants, in particular N-acetylcysteine, have been reported in small studies to reduce the frequency of exacerbations, leading to speculations that these medications could have a role in the treatment of patients with recurrent exacerbations (**Evidence B**). However, a large randomized controlled trial found no effect of N-acetylcysteine on the frequency of exacerbations, except in patients not treated with inhaled glucocorticosteroids.
NCCCC/NICE (2004)	**A** - Treatment with alpha-tocopherol and beta-carotene supplements, alone or in combination, is not recommended.
SMOH (2006)	**V. Others** There is no evidence to date to support the benefit of the routine use of maintenance antibiotic therapy, mucolytics/anti-oxidants respiratory stimulants, vasodilators, nedocromil sodium or leukotriene modifiers in stable COPD.
Antitussives	
FMS (2007)	No recommendations offered.

GOLD (2007)	Cough, although sometimes a troublesome symptom in COPD, has a significant protective role. Thus, the regular use of antitussives is not recommended in stable COPD (**Evidence D**).
NCCCC/NICE (2004)	**D** - Antitussive therapy should not be used in the management of stable COPD.
SMOH (2006)	No recommendations offered.
NON-PHARMACOLOGIC TREATMENTS	
Long-term Oxygen Therapy (LTOT)	

FMS (2007)	**<u>Oxygen Therapy at Home</u>**
	
	Basics
	
	• Oxygen therapy at home can be used to prevent elevation of pulmonary arterial pressure in advanced COPD and to extend the life of the patient.
	• The effect of oxygen therapy on symptoms (e.g., shortness of breath) is quite limited.
	• Oxygen therapy at home is meant only for patients with chronic hypoxaemia (i.e., arterial desaturation).
	• Treatment decisions should be made after critical consideration.
	• When initiating oxygen therapy at home, appropriate monitoring of treatment must be ensured. Treatment decisions and implementation of treatment are the responsibility of the local pulmonary clinic.
	
	Initiation Criteria for Oxygen Therapy
	
	• Chronic, advanced pulmonary disease (FEV_1 <1.5 L)
	• The partial pressure of oxygen in arterial blood, measured with the patient in a stable phase of the disease breathing room air <7.3 kPa in two samples taken with an interval of at least three weeks.
	• Partial pressure of oxygen can also be 7.3 to 8.0 kPa if one of the following criteria is involved:
	  • Signs of increased pulmonary arterial pressure (e.g., oedema)
	  • Secondary polycythaemia (haematocrit >55)
	  • Significant nocturnal hypoxaemia established by oximetry and reversible by oxygen therapy and not caused by concomitant sleep apnoea syndrome
	  • Significant neuropsychological symptoms reversible by oxygen therapy

	• Oxygen therapy gives the desired response (PaO_2 >8.0 kPa) without unfavourable increase in the partial pressure of carbon dioxide in arterial blood. • The patient does not smoke and is sufficiently co-operative. **Implementation of Treatment** • Oxygen therapy at home is implemented in most cases using an electric oxygen concentrator. The oxygen concentrator eliminates nitrogen from room air and provides the patient with over 90%-proof oxygen. • Portable liquid oxygen is suitable for certain patients. Primarily these are patients who are in the working life and/or who are motivated for rehabilitation through physical exercise. • All oxygen therapy necessitates good co-operation by the patient and willingness for long-term co-operation with the treating unit. • Home calls made by a rehabilitation instructor are an essential part of the monitoring of patients receiving oxygen therapy at home.
GOLD (2007)	**Key Points**: • The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival (**Evidence A**). **Oxygen Therapy** Oxygen therapy, one of the principal nonpharmacologic treatments for patients with *Stage IV: Very Severe COPD*, can be administered in three ways: long-term continuous therapy, during exercise, and to relieve acute dyspnea. The primary goal of oxygen therapy is to increase the baseline PaO_2 to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce an SaO_2 at least 90%, which will preserve vital organ function by ensuring adequate delivery of oxygen. LTOT is generally introduced in *Stage IV: Very Severe COPD* for patients who have: • PaO_2 at or below 7.3 kPa (55 mm Hg) or SaO_2 at or below 88%, with or without hypercapnia (**Evidence B**); or • PaO_2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg) or SaO_2 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%)

	(**Evidence D**). A decision about the use of LTOT should be based on the waking PaO_2 values. The prescription should always include the source of supplemental oxygen (gas or liquid), method of delivery, duration of use, and the flow rate at rest, during exercise, and during sleep. A detailed review of the uses of oxygen in COPD, together with possible assessment algorithms and information about methods of delivery, is available from http://www.thoracic.org. A number of physiological studies have shown that delivering oxygen during exercise can increase the duration of endurance exercise and/or reduce the intensity of end-exercise breathlessness (**Evidence A**). Oxygen therapy reduces the oxygen cost of breathing and minute ventilation, a mechanism that although still disputed helps to minimize the sensation of dyspnea. This has led to the use of short burst therapy to control severe dyspnea such as occurs after climbing stairs. However, there is no benefit from using short burst oxygen for symptomatic relief before or after exercise (**Evidence B**). ***Oxygen use in air travel.*** Although air travel is safe for most patients with chronic respiratory failure who are on long-term oxygen therapy, patients should be instructed to increase the flow by 1 to 2 L/min during the flight. Ideally, patients who fly should be able to maintain an in-flight PaO_2 of at least 6.7 kPa (50 mm Hg). Studies indicate that this can be achieved in those with moderate to severe hypoxemia at sea level by supplementary oxygen at 3 L/min by nasal cannulae or 31% by Venturi facemask. Those with a resting PaO_2 at sea level of > 9.3 kPa (70 mm Hg) are likely to be safe to fly without supplementary oxygen, although it is important to emphasize that a resting PaO_2 > 9.3 kPa (70 mm Hg) at sea level does not exclude the development of severe hypoxemia when travelling by air (**Evidence C**).
NCCCC/NICE (2004)	**Long-term Oxygen Therapy (LTOT)** **C** - Clinicians should be aware that inappropriate oxygen therapy in people with COPD may cause respiratory depression. **A** - LTOT is indicated in patients with COPD who have a PaO_2 less than 7.3 kPa when stable or a PaO_2 greater than 7.3 and less than 8 kPa when stable and one of: secondary polycythaemia, nocturnal hypoxaemia (oxygen saturation of

arterial blood [SaO_2] less than 90% for more than 30% of time), peripheral oedema, or pulmonary hypertension.

A - To get the benefits of LTOT patients should breathe supplemental oxygen for at least 15 hours per day. Greater benefits are seen in patients receiving oxygen for 20 hours per day.

D - The need for oxygen therapy should be assessed in:

- All patients with severe airflow obstruction (FEV_1 less than 30% predicted)
- Patients with cyanosis
- Patients with polycythaemia
- Patients with peripheral oedema
- Patients with a raised jugular venous pressure
- Patients with oxygen saturations less than or equal to 92% breathing air

Assessment should also be considered in patients with moderate airflow obstruction (FEV_1 30 to 49% predicted).

D - To ensure all patients eligible for LTOT are identified, pulse oximetry should be available in all healthcare settings.

D - The assessment of patients for LTOT should comprise the measurement of arterial blood gasses on two occasions at least 3 weeks apart in patients who have a confident diagnosis of COPD, who are receiving optimum medical management, and whose COPD is stable.

D - Patients receiving LTOT should be reviewed at least once per year by practitioners familiar with LTOT, and this review should include pulse oximetry.

D - Oxygen concentrators should be used to provide the fixed supply at home for long-term oxygen therapy.

D - Patients should be warned about the risks of fire and explosion if they continue to smoke when prescribed oxygen.

Ambulatory Oxygen Therapy

D - People who are already on LTOT who wish to continue with oxygen therapy outside the home, and who are prepared to use it, should have ambulatory oxygen prescribed.

D - Ambulatory oxygen therapy should be considered in patients who have exercise desaturation, are shown to have an improvement in exercise capacity and/or dyspnoea with

	oxygen, and have the motivation to use oxygen. **D** - Ambulatory oxygen therapy is not recommended in COPD if PaO_2 is greater than 7.3 kPa and there is no exercise desaturation. **D** - Ambulatory oxygen therapy should only be prescribed after an appropriate assessment has been performed by a specialist. The purpose of the assessment is to assess the extent of desaturation, the improvement in exercise capacity with supplemental oxygen, and the oxygen flow rate required to correct desaturation, aiming to keep the SaO_2 above 90%. **D** - Small light-weight cylinders, oxygen-conserving devices, and portable liquid oxygen systems should be available for the treatment of patients with COPD. **D** - A choice about the nature of equipment prescribed should take account of the hours of ambulatory oxygen use required by the patient and the oxygen flow rate required. (See Table 12 in the original guideline document for a list of appropriate equipment for ambulatory oxygen therapy.) **Short-burst Oxygen Therapy** **C** - Short-burst oxygen therapy should only be considered for episodes of severe breathlessness in patients with COPD not relieved by other treatments. **D** - Short-burst oxygen therapy should only continue to be prescribed if an improvement in breathlessness following therapy has been documented. **D** - When indicated, short-burst oxygen should be provided from cylinders.
SMOH (2006)	**Oxygen Therapy in Chronic Obstructive Pulmonary Disease** **A** - Patients with very severe COPD and chronic respiratory failure should be assessed for the need for long-term oxygen therapy. (**Grade A, Level 1+**) **A** - Indications for long-term oxygen therapy (at least 15 hours/day) in patients with COPD should be based on the following indices obtained in stable state: • Without pulmonary hypertension (Cor Pulmonale), congestive heart failure, polycythaemia (Hct >55%): 1. $PaO_2 \leq$ 55 mmHg on Room Air

	OR 2. $SaO_2 \leq$ 89% on Room Air • With pulmonary hypertension (Cor Pulmonale), congestive heart failure, polycythaemia (Hct >55%): 1. PaO_2 between 55 mmHg — 60 mmHg on Room Air OR 2. $SaO_2 \leq$ 89% on Room Air **(Grade A, Level 1+)** **D** - Oxygen concentrator is the preferred mode of delivery of oxygen. It is the most convenient and economical method of providing long-term oxygen therapy. (**Grade D, Level 3**) **D** - Very severe COPD patients with hypercapnic respiratory failure requiring long-term oxygen therapy should have the oxygen flow rate titrated cautiously to maintain a $SaO_2 \geq$ 90%. (**Grade D, Level 4**)
Lifestyle Modification	
FMS (2007)	**Cessation of Smoking** • The most essential factor regarding the prognosis • Does not normalize lung function, but the progressive deterioration of FEV_1 slows down and proceeds at the same pace as in nonsmokers. • According to present knowledge, there is no drug therapy available that could essentially delay the deterioration of lung function if the patient continues smoking. Drugs are useful only for relieving subjective symptoms and in the treatment of acute exacerbations.
GOLD (2007)	**Key Points**: • Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of COPD. • Smoking cessation is the single most effective—and cost effective—intervention in most people to reduce the risk of developing COPD and stop its progression (**Evidence A**). • Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel. • Efforts to reduce smoking through public health initiatives

should also focus on passive smoking to minimize risks for nonsmokers.

- Many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases.
- Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy and protective steps taken by individual patients.

Smoking Cessation

The Public Health Service Guidelines recommend a five-step program for intervention (Figure 5.2-3 in the original guideline document), which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking. The guidelines emphasize that tobacco dependence is a chronic disease (Figure 5.2-4 in the original guideline document) and urge clinicians to recognize that relapse is common and reflects the chronic nature of dependence and addiction, not failure on the part of the clinician or the patient.

Most individuals go through several stages before they stop smoking (Figure 5.2-5 in the original guideline document). It is often helpful for the clinician to assess a patient's readiness to quit in order to determine the most effective course of action at that time. The clinician should initiate treatment if the patient is ready to quit. For a patient not ready to make a quit attempt, the clinician should provide a brief intervention designed to promote the motivation to quit.

Counseling. Counseling delivered by physicians and other health professionals significantly increases quit rates over self-initiated strategies. Even a brief (3-minute) period of counseling to urge a smoker to quit results in smoking cessation rates of 5 to 10%. At the very least, this should be done for every smoker at every health care provider visit. Education in how to offer optimal smoking cessation advice and support should be a mandatory element of curricula for health professionals.

Pharmacotherapy. Numerous effective pharmacotherapies for smoking cessation now exist, and pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. Special consideration should be given before using pharmacotherapy in selected populations: people with medical contraindications, light smokers (fewer than 10 cigarettes/day), and pregnant and adolescent smokers.

(Refer to the original guideline for specific recommendations regarding pharmacotherapy.)

NCCCC/NICE (2004)	**D** - An up-to-date smoking history, including pack years smoked (number of cigarettes smoked per day, divided by 20, multiplied by the number of years smoked), should be documented for everyone with COPD. **A** - All COPD patents still smoking, regardless of age, should be encouraged to stop, and offered help to do so, at every opportunity. **B** - Unless contraindicated, bupropion or nicotine replacement therapy (NRT) combined with an appropriate support programme should be used to optimise smoking quit rates for people with COPD. **NICE** - NICE Technology Appraisal Guidance No 39 (see Section 6 of the original guideline document) recommends: *"If a smoker's attempt to quit is unsuccessful with treatment using either nicotine replacement therapy or bupropion, the National Health Service should normally fund no further attempts within 6 months. However, if external factors interfere with a person's initial attempt to stop smoking, it may be reasonable to try again sooner."*
SMOH (2006)	**Nutrition in COPD** **D** - All patients with COPD should undergo simple nutrition screening. **(Grade D, Level 4)** **GPP** - Nutritional intervention should be considered in all COPD patients with BMI <18.5 kg/m2 or significant involuntary weight loss (>10% during the last 6 months or >5% in the past month). **(GPP)** **Smoking Cessation** **A** - Smoking cessation should be emphasized as an essential first step in management of COPD patients. **(Grade A, Level 1++)** **GPP** - Clinicians should play a prominent role in promoting attempts to stop smoking in their patients. **(GPP)** **A** - All smokers, including those who may be at risk for COPD as well as those who already have the disease, should be offered at least a brief tobacco dependence counseling at every health care provider visit. **(Grade A, Level 1++)**

	Pharmacotherapy **D** - Pharmacotherapy for smoking cessation is recommended when counseling is not sufficient to help patients quit smoking. **(Grade D, Level 4)** **A** - Treatment of nicotine dependence is effective and should be offered to smokers in addition to counselling. **(Grade A, Level 1++)** In Singapore, there are four types of pharmacotherapies for tobacco dependence available currently i.e. bupropion SR, nicotine gum, nicotine inhaler, and nicotine patch. **A** - These pharmacotherapies reliably increase long-term smoking abstinence rates and at least one of these medications should be added to counseling if necessary and in the absence of. **(Grade A, Level 1++)**
Patient Education	
FMS (2007)	No recommendations offered
GOLD (2007)	**Key Points**: • For patients with COPD, health education plays an important role in smoking cessation (**Evidence A**) and can also play a role in improving skills, ability to cope with illness and health status. Studies that have been done indicate that patient education alone does not improve exercise performance or lung function (**Evidence B**), but it can play a role in improving skills, ability to cope with illness, and health status. These outcomes are not traditionally measured in clinical trials, but they may be most important in COPD where even pharmacologic interventions generally confer only a small benefit in terms of lung function. Patient education regarding smoking cessation has the greatest capacity to influence the natural history of COPD. Evaluation of the smoking cessation component in a long-term, multicenter study indicates that if effective resources and time are dedicated to smoking cessation, 25% long-term quit rates can be maintained (**Evidence A**). Education also improves patient response to exacerbations (**Evidence B**). Prospective end-of-life discussions can lead to understanding of advance directives and effective therapeutic decisions at

the end of life (**Evidence B**).

Ideally, educational messages should be incorporated into all aspects of care for COPD and may take place in many settings: consultations with physicians or other health care workers, home-care or outreach programs, and comprehensive pulmonary rehabilitation programs.

Components of an Education Program

The topics that seem most appropriate for an education program include: smoking cessation; basic information about COPD and pathophysiology of the disease; general approach to therapy and specific aspects of medical treatment; self-management skills; strategies to help minimize dyspnea; advice about when to seek help; self-management and decision-making during exacerbations; and advance directives and end-of-life issues (Figure 5.3-2 — see below). Education should be part of consultations with health care workers beginning at the time of first assessment for COPD and continuing with each follow-up visit. The intensity and content of these educational messages should vary depending on the severity of the patient's disease. In practice, a patient often poses a series of questions to the physician (Figure 5.3-3 in the original guideline document). It is important to answer these questions fully and clearly, as this may help make treatment more effective.

Topics for Patient Education (figure 5.3-2 in the original guideline document)

For all patients:

- Information and advice about reducing risk factors

Stage I: Mild COPD through Stage III: Severe COPD

Above topic, plus:

- Information about the nature of COPD
- Instruction on how to use inhalers and other treatments
- Recognition and treatment of exacerbations
- Strategies for minimizing dyspnea

Stage IV: Very Severe COPD

Above topics, plus:

- Information about complications
- Information about oxygen treatment

	• Advance directives and end-of-life decisions

NCCCC/NICE (2004)	**A** - There are significant differences in the response of patients with COPD and asthma to education programmes. Programmes designed for asthma should not be used in COPD.
	
	D - Specific educational packages should be developed for patients with COPD.
	
	• Suggested topics for inclusion are:
	  • Disease education (anatomy, physiology, pathology and pharmacology, including oxygen therapy & vaccination)
	  • Dyspnea/symptom management, including chest clearance techniques
	  • Smoking cessation
	  • Energy conservation/pacing
	  • Nutritional advice
	  • Managing travel
	  • Benefits system and disabled parking badges
	  • Advance directives (living wills)
	  • Making a change plan
	  • Anxiety management
	  • Goal setting and rewards
	  • Relaxation
	  • Identifying and changing beliefs about exercise and health related behaviors
	  • Loving relationships/sexuality
	  • Exacerbation management (including when to seek help, self-management and decision making, coping with setbacks and relapses)
	  • Home care support
	  • Managing surgery (non thoracic)
	  • The benefits of physical exercise
	  • Support groups
	• The packages should take account of the different needs of patients at different stages of their disease.
	
	D - Patients with moderate and severe COPD should be made aware of the technique of non-invasive ventilation (NIV). Its benefits and limitations should be explained so that, if it is ever necessary in the future, they will be aware of these issues.

SMOH (2006)	**Patient Education** **D** - Patient education is a vital part of COPD management and should begin at the time of first assessment for COPD and

	continue with each follow-up visit (**Grade D, Level 4**) **D** - The intensity and content of patient educational messages should vary depending on the severity of the patient's disease (see Table 8 in the original guideline document). **D** - Patient education should be: • Tailored to meet the needs of the individual patient • Interactive • Directed to improving quality of life • Simple to follow • Practical • Appropriate to the intellectual and social skill of the patient and the caregivers **(Grade D, Level 4)** **End of Life Care in COPD** **D** - Patients should be educated about their disease, prognosis and possible circumstances of death. (**Grade D, Level 3**) **D** - Physicians should discuss end of life issues and advance care planning with patients (and their relatives) who have severe to very severe COPD. (**Grade D, Level 3**) **B** - Physicians who look after severe to very severe COPD patients (as with all physicians caring for the terminally ill) will need to be prepared to discuss end of life issues with patients. (**Grade B, Level 1+**)
Surgery	
FMS (2007)	Surgery (bullectomy, lung transplantation, lung volume reduction) can be recommended only to a small subset of the patients after careful evaluation.
GOLD (2007)	***Bullectomy***. Bullectomy is an older surgical procedure for bullous emphysema. Removal of a large bulla that does not contribute to gas exchange decompresses the adjacent lung parenchyma. Bullectomy can be performed thoracoscopically. In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function (**Evidence C**). ***Lung volume reduction surgery (LVRS)***. LVRS is a surgical procedure in which parts of the lung are resected to reduce hyperinflation, making respiratory muscles more effective pressure generators by improving their mechanical efficiency (as measured by length/tension relationship, curvature of the

	diaphragm, and area of apposition). In addition, LVRS increases the elastic recoil pressure of the lung and thus improves expiratory flow rates. ***Lung transplantation***. In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity (**Evidence C**), although the Joint United Network for Organ Sharing in 1998 found that lung transplantation does not confer a survival benefit in patients with endstage emphysema after two years. Criteria for referral for lung transplantation include FEV_1 < 35% predicted, PaO_2 < 7.3 to 8.0 kPa (55 to 60 mm Hg), $PaCO_2$ > 6.7 kPa (50 mm Hg), and secondary pulmonary hypertension. **Note:** Refer to the original guideline document for a discussion of postoperative pulmonary complications.
NCCCC/NICE (2004)	**C** - Patients who are breathless and have a single large bulla on a CT scan and an FEV_1 less than 50% predicted should be referred for consideration of bullectomy. **A** - Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living, despite maximal medical therapy (including rehabilitation), should be referred for consideration of lung volume reduction surgery if they meet all of the following criteria: • FEV_1 more than 20% predicted • $PaCO_2$ less than 7.3 kPa • Upper lobe predominant emphysema • T_LCO more than 20% predicted **C** - Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living despite maximal medical therapy should be considered for referral for assessment for lung transplantation, bearing in mind comorbidities and local surgical protocols. Considerations include: • Age • FEV_1 • $PaCO_2$ • Homogeneously distributed emphysema on CT scan • Elevated pulmonary artery pressures with progressive deterioration
SMOH (2006)	**Surgical Options for COPD Patients**

There are a variety of surgical options available for patients with COPD. These options are primarily focused at improving symptoms and restoring function in a select group of COPD patients.

The surgical options available are:

1. Bullectomy
2. Lung Volume Reduction Surgery
3. Lung Transplantation

Bullectomy

Surgical removal of large bullae in COPD patients may improve symptoms, exercise tolerance and pulmonary function.

D - Selection of patients with giant bullae who will benefit from bullectomy should be based on clinical, radiological and pulmonary physiological parameters as indicated below (refer to the original guideline document for parameters). (**Grade D, Level 3**)

Lung Volume Reduction Surgery (LVRS)

Overall LVRS has been shown to improve FEV_1, exercise tolerance, quality of life and may be long-term survival. The effect of LVRS seems to be maximal at 6 months post surgery.

A - Selection of patients that will benefit from LVRS is based on the following indications and contraindications (refer to the original guideline document) (**Grade A, Level 1+**)

Investigations for patients being considered for LVRS include the following:

1. High resolution computed tomography thorax
2. Pulmonary Function Test including Diffusion Capacity
3. Arterial Blood gas
4. Cycle ergometry to determine exercise capacity post-pulmonary rehabilitation
5. 2D-echocardiogram or right heart catheter study to determine pulmonary arterial pressure.

GPP - LVRS and lung transplantation are surgical options, which are usually considered in selected patients with advanced COPD unresponsive to medical therapy. These patients should be referred to specialty centres where these procedures are done for further evaluation.

Lung Transplantation

COPD is the most common indication for lung transplantation.

The choice of bilateral lung transplantation (BLT) or single lung transplantation (SLT) for COPD remains controversial. Bilateral lung transplantation results in greater improvement in FEV_1, but improvements in exercise capacity are not always significantly greater than SLT.

Lung transplantation leads to improvement in FEV_1, exercise capacity and quality of life.

D - Lung transplantation should be considered in selected patients with end-stage COPD. Refer to the original guideline document for selection criteria. (**Grade D, Level 3 & 4**)

Compared to patients with other cardiopulmonary disease, patients with COPD exhibit the best overall survival after lung transplantation.

Surgery in COPD Patients

GPP - Preoperative assessment of a COPD patient should include:

1. Detailed history and physical examination
2. Assessment of functional capacity (American Society of Anesthesiology Physical Status Scale). See Table 10 in the original guideline document.
3. Preoperative Spirometry
4. Arterial Blood Gas especially in moderate to severe COPD
5. Chest Radiograph

(GPP)

A - COPD patients being considered for surgery should be assessed for risk of developing venous thromboembolism and also for thromboprophylaxis during the perioperative assessment. (**Grade A, Level 1+**)

A - Combination of bronchodilators, chest physiotherapy, antibiotics, smoking cessation for at least 4 to 8 weeks and a short course of oral corticosteroids should be given for patients with acute exacerbation so as to reduce the risk of postoperative pulmonary complications. (**Grade A Level 1+**)

COPD patients who have symptoms and signs of airflow obstruction should be treated aggressively. Elective surgery in these patients should be deferred especially if the patient has

	an acute exacerbation.
ONGOING ASSESSMENT AND FOLLOW-UP	
FMS (2007)	No recommendations offered.
GOLD (2007)	**Ongoing Monitoring and Assessment** Visits to health care facilities will increase in frequency as COPD progresses. The type of health care workers seen, and the frequency of visits, will depend on the health care system. Ongoing monitoring and assessment in COPD ensures that the goals of treatment are being met and should include evaluation of: (1) exposure to risk factors, especially tobacco smoke; (2) disease progression and development of complications; (3) pharmacotherapy and other medical treatment; (4) exacerbation history; (5) comorbidities. Suggested questions for follow-up visits are listed in Figure 5.1-8 of the original guideline document. The best way to detect changes in symptoms and overall health status is to ask the patient the same questions at each visit. **Monitor Disease Progression and Development of Complications** COPD is usually a progressive disease. Lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy and to identify any complications that may develop. As at the initial assessment, follow-up visits should include a physical examination and discussion of symptoms, particularly any new or worsening symptoms. ***Pulmonary function***. A patient's decline in lung function is best tracked by periodic spirometry measurements although useful information about lung function decline is unlikely from spirometry measurements performed more than once a year. Spirometry should be performed if there is a substantial increase in symptoms or a complication. Other pulmonary function tests, such as flow-volume loops, diffusing capacity (D_{LCO}) measurements, inspiratory capacity, and measurement of lung volumes are not needed in a routine assessment but can provide information about the overall impact of the disease and can be valuable in resolving diagnostic uncertainties and assessing patients for surgery. ***Arterial blood gas measurement***. The development of respiratory failure is indicated by a PaO_2 < 8.0 kPa (60 mm

Hg) with or without $PaCO_2$ > 6.7 kPa (50 mm Hg) in arterial blood gas measurements made while breathing air at sea level. Screening patients by pulse oximetry and assessing arterial blood gases in those with an oxygen saturation (SaO_2) < 92% is a useful way of selecting patients for arterial blood gas measurement. However, pulse oximetry gives no information about CO_2 tensions. Clinical signs of respiratory failure or right heart failure include central cyanosis, ankle swelling, and an increase in the jugular venous pressure. Clinical signs of hypercapnia are extremely nonspecific outside of exacerbations.

Assessment of pulmonary hemodynamics. Mild to moderate pulmonary hypertension (mean pulmonary artery pressure $\geq$ 30 mm Hg) is only likely to be important in patients who have developed respiratory failure. Measurement of pulmonary arterial pressure is not recommended in clinical practice as it does not add practical information beyond that obtained from a knowledge of PaO_2.

Diagnosis of right heart failure or cor pulmonale. Elevation of the jugular venous pressure and the presence of pitting ankle edema are often the most useful findings suggestive of cor pulmonale in clinical practice. However, the jugular venous pressure is often difficult to assess in patients with COPD, due to large swings in intrathoracic pressure. Firm diagnosis of cor pulmonale can be made through a number of investigations, including radiography, electrocardiography, echocardiography, radionucleotide scintigraphy, and magnetic resonance imaging. However, all of these measures involve inherent inaccuracies of diagnosis.

CT and ventilation-perfusion scanning. Despite the benefits of being able to delineate pathological anatomy, routine CT and ventilation-perfusion scanning are currently confined to the assessment of COPD patients for surgery. HRCT is currently under investigation as a way of visualizing airway and parenchymal pathology more precisely.

Hematocrit. Polycythemia can develop in the presence of arterial hypoxemia, especially in continuing smokers, and can be identified by hematocrit > 55%. Anemia is more prevalent than previously thought, affecting almost a quarter of COPD patients in one hospital series. A low hematocrit indicates a poor prognosis in COPD patients receiving long-term oxygen treatment.

Respiratory muscle function. Respiratory muscle function is usually measured by recording the maximum inspiratory and expiratory mouth pressures. More complex measurements are confined to research laboratories. Measurement of inspiratory

muscle force is useful in assessing patients when dyspnea or hypercapnia is not readily explained by lung function testing or when peripheral muscle weakness is suspected. This measurement may improve in COPD patients when other measurements of lung mechanics do not (e.g., after pulmonary rehabilitation).

Sleep studies. Sleep studies may be indicated when hypoxemia or right heart failure develops in the presence of relatively mild airflow limitation or when the patient has symptoms suggesting the presence of sleep apnea.

Exercise testing. Several types of tests are available to measure exercise capacity (e.g., treadmill and cycle ergometry in the laboratory — or six-minute and shuttle walking tests) but these are primarily used in conjunction with pulmonary rehabilitation programs.

Monitor Pharmacotherapy and Other Medical Treatment

In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Dosages of various medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and side effects of treatment should be monitored.

Monitor Exacerbation History

During periodic assessments, health care workers should question the patient and evaluate any records of exacerbations, both self-treated and those treated by other health care providers. Frequency, severity, likely causes of exacerbations, and the patient's psychological well-being should be evaluated. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted. Specific inquiry into unscheduled visits to providers, telephone calls for assistance, and use of urgent or emergency care facilities may be helpful. Severity can be estimated by the increased need for bronchodilator medication or glucocorticosteroids and by the need for antibiotic treatment. Hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or intubation. The clinician then can request summaries of all care received to facilitate continuity of care.

Monitor Comorbidities

Comorbidities are common in COPD. Some may be an indirect result of COPD, arising independently but more likely to occur

	when COPD is present, e.g., ischemic heart disease, bronchial carcinoma, osteoporosis, and depression. Other comorbid conditions may coexist with COPD because they become prevalent as part of the aging process, e.g., arthritis, diabetes, reflux esophagitis. All comorbid conditions become harder to manage when COPD is present, either because COPD adds to the total level of disability or because COPD therapy adversely affects the comorbid disorder. All comorbid conditions amplify the disability associated with COPD and can potentially complicate its management. Until more integrated guidance about disease management for specific comorbid problems becomes available, the focus should be on identification and management of these individual problems in line with local treatment guidance.

NCCCC/NICE (2004)	**D** - Follow-up of all patients with COPD should include:
	
	• Highlighting the diagnosis of COPD in the case record and recording this using Read codes on a computer database
	• Recording the values of spirometric tests performed at diagnosis (both absolute and percent predicted)
	• Offering smoking cessation advice
	• Recording the opportunistic measurement of spirometric parameters (a loss of 500 mL or more over 5 years will select out those patients with rapidly progressing disease who may need specialist referral and investigation)
	
	D - Patients with mild or moderate COPD should be reviewed at least once per year, or more frequently if indicated, and the review should cover the issues listed below and in Table 14 of the original guideline document.
	
	• Clinical assessment
	  • Smoking status and desire to quit
	  • Adequacy of symptom control
	  • Breathlessness
	  • Exercise tolerance
	  • Estimated exacerbation frequency
	  • Presence of complications
	  • Effects of each drug treatment
	  • Inhaler technique
	  • Need for referral to specialist and therapy services
	  • Need for pulmonary rehabilitation
	• Measurements to make
	  • FEV_1 & FVC
	  • BMI
	  • MRC dyspnoea score
	
	D - For most patients with stable severe disease, regular hospital review is not necessary, but there should be locally agreed mechanisms to allow rapid access to hospital

	assessment when necessary
	
	D - When patients with severe COPD are reviewed in primary care, they should be seen at least twice a year, and specific attention should be paid to the issues listed below and in Table 14 of the original guideline document:
	
	• Clinical assessment
	  • Smoking status & desire to quit
	  • Adequacy of symptom control
	  • Breathlessness
	  • Exercise tolerance
	  • Estimated exacerbation frequency
	  • Presence of cor pulmonale
	  • Need for long-term oxygen therapy
	  • Patient's nutritional state
	  • Presence of depression
	  • Effects of each drug treatment
	  • Inhaler technique
	  • Need for Social Services & Occupational Therapy input
	  • Need for referral to specialist and therapy services
	  • Need for pulmonary rehabilitation
	• Measurements to make
	  • FEV_1 & FVC
	  • BMI
	  • MRC dyspnoea score
	  • SaO_2
	
	D - Patients with severe disease requiring interventions such as long-term noninvasive ventilation should be reviewed regularly by specialists.

SMOH (2006)	**Monitoring of Patients with Stable COPD** **D & GPP** - Patients should be seen and assessed regularly (e.g., three monthly in the stable state). At each follow-up visit: • Patients should be asked regarding onset of any new symptoms and/or worsening of exercise capacity. • Current smokers should be given repeated advice to quit. • Adherence to medications should be assessed, and the patient's inhaler technique checked and re-taught if necessary. (**Grade D, Level 4/GPP**)

	D & GPP - Indications for specialist referral: • Severe COPD (FEV_1 < 50% predicted). • Frequent exacerbations (e.g., two or more a year) despite compliance to treatment. • Rapidly progressive course of the disease. • Development of new symptoms (e.g., haemoptysis) or new physical signs (e.g., cyanosis, peripheral oedema). (**Grade D, Level 4/GPP**)

TABLE 4: BENEFITS AND HARMS	
Benefits	
FMS (2007)	Appropriate management and treatment of COPD may help relieve patient symptoms, improve exercise capacity, improve lung function, reduce morbidity and mortality, improve quality of life, and reduce frequency and severity of exacerbations.

GOLD (2007)	**Overall Benefits of Guideline Recommendations**
	
	• The goals of effective COPD management are to:
	  • Prevent disease progression
	  • Relieve symptoms
	  • Improve exercise tolerance
	  • Improve health status
	  • Prevent and treat complications
	  • Prevent and treat exacerbations
	  • Reduce mortality
	• COPD prevention

NCCCC/NICE (2004)	If adopted, the guideline recommendations should lead to better standards of care and thus better outcomes from chronic obstructive pulmonary disease.
SMOH (2006)	Appropriate diagnosis and management of patients with COPD
Harms	
FMS (2007)	• Common adverse effects of oral, long-acting theophylline include central nervous system and gastrointestinal symptoms. Arrhythmias and convulsions are signs of toxicity.

	• Adverse drug reactions of ipratropium bromide included dry mouth and tremor.
GOLD (2007)	**Arterial Blood Gas Measurement**: Adequate pressure must be applied at the arterial puncture site for at least one minute, as failure to do so can lead to painful bruising. **Beta$_2$-agonists**: Stimulation of beta$_2$-receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta$_2$-agonists, whatever the route of administration, and this limits the dose that can be tolerated. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics, and oxygen consumption can be increased under resting conditions, these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 occur after administration of both short- and long-acting beta$_2$-agonists, but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago, further detailed study has found no association between beta$_2$-agonist use and an accelerated loss of lung function or increased mortality in COPD. **Anticholinergics**: Anticholinergic drugs are poorly absorbed, which limits the troublesome systemic effects seen with atropine. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 micrograms a day as a dry powder, does not retard mucus clearance from the lungs. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. A bitter, metallic taste is reported by some patients using ipratropium. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and requires further investigation. Use of wet nebulizer solutions with a face mask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye. Mucociliary clearance is unaffected by theses drugs, and respiratory infection rates are not increased. **Methylxanthines**: Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide

	range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental). **Oral Glucocorticosteroids**: A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced COPD. **Narcotics (morphine)**: Some clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects. **Lung Transplantation**: The common complications seen in COPD patients after lung transplantation, apart from operative mortality, are acute rejection and bronchiolitis obliterans, cytomegalovirus (CMV), other opportunistic fungal (Candida, Aspergillus, Cryptococcus, Carinii) or bacterial (Pseudomonas, Staphylococcus species) infections, lymphoproliferative disease, and lymphomas. **Invasive Mechanical Ventilation**: Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.
NCCCC/NICE (2004)	• Particular caution needs to be taken with the use of theophylline in elderly patients because of differences in pharmacokinetics, the increased likelihood of comorbidities, and the use of other medications. • Clinicians should be aware of the potential risk of developing osteoporosis and other side effects in patients treated with high-dose inhaled corticosteroids (especially in the presence of other risk factors) and should discuss the risk with patients. • Patients should be warned about the risks of fire and explosion if they continue to smoke when prescribed oxygen. • The technology appraisal also notes that zanamivir should be used with caution in people with COPD because of risk of bronchospasm. If people with COPD are prescribed zanamivir they should be made aware of the risks and have a fast-acting bronchodilator available. • Care should be taken when using intravenous theophylline because of interactions with other drugs and potential

	toxicity if the patient has been on oral theophylline.
SMOH (2006)	• Side effects of medication • Complications related to surgery • Risk of fire and explosion when using oxygen therapy. Patients requiring oxygen therapy should be advised against smoking cigarettes.

TABLE 5: EVIDENCE RATING SCHEMES AND REFERENCES	
FMS (2007)	**Classification of the Quality of Evidence** A. **Quality of Evidence: High.** • Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multi-centre trial B. **Quality of Evidence: Moderate.** • Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations C. **Quality of Evidence: Low.** • Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations D. **Quality of Evidence: Very Low.** • Any estimate of effect is very uncertain. • Expert opinion • No direct research evidence • One or more studies with very severe limitations
GOLD (2007)	**Levels of Evidence** A. Randomized controlled trials. Rich body of data. *Definition:* Evidence is from endpoints of well-designed

	randomized controlled trials that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants. B. Randomized controlled trials. Limited data. *Definition:* Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of randomized controlled trials, or meta-analysis of randomized controlled trials. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent. C. Nonrandomized trials. Observational studies. *Definition:* Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies. D. Panel consensus. Judgment. *Definition:* This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.
NCCCC/NICE (2004)	**Levels of Evidence** **Ia**: Evidence from systematic reviews or meta-analysis of randomised controlled trials **Ib**: Evidence from at least one randomised controlled trial **IIa**: Evidence from at least one controlled study without randomisation **IIb**: Evidence from at least one other type of quasi-experimental study **III**: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies **IV**: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities **NICE**: Evidence from NICE guidelines or Health Technology

	Appraisal Programme **HSC**: Evidence from Health Service Circulars **Grading of Recommendations** A. Based on hierarchy I evidence B. Based on hierarchy II evidence or extrapolated from hierarchy I evidence C. Based on hierarchy III evidence or extrapolated from hierarchy I or II evidence D. Directly based on hierarchy IV evidence or extrapolated from hierarchy I, II, or III evidence
SMOH (2006)	**Grades of Recommendations** **Grade A**: At least one meta-analysis, systematic review of randomized controlled trials (RCTs), or RCT rated as 1+ + and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results **Grade B**: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1+ + or 1+ **Grade C**: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2+ + **Grade D**: Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ **GPP (good practice points)**: Recommended best practice based on the clinical experience of the guideline development group. **Levels of Evidence** **Level 1++**: High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very

	low risk of bias. **Level 1+**: Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias. **Level 1-**: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias **Level 2++**: High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal **Level 2+**: Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal **Level 2-**: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal **Level 3**: Non-analytic studies (e.g., case reports, case series) **Level 4**: Expert opinion

GUIDELINE CONTENT COMPARISON

The Finnish Medical Society Duodecim (FMS), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (a collaborative project of the World Health Organization/and National Heart, Lung, and Blood Institute), the National Collaborating Centre for Chronic Conditions (a collaborating center for the National Institute for Health and Clinical Excellence [NCCCC/NICE]), and the Singapore Ministry of Health (SMOH) present recommendations for the diagnosis and management of stable COPD and provide explicit reasoning behind their judgments. All four guidelines identify the type of supporting evidence for selected recommendations. The FMS and GOLD guidelines are updates of previous versions. In developing their guidelines both GOLD and SMOH reviewed the 2004 NCCCC/NICE guideline. SMOH also reviewed the 2005 version of the GOLD guideline.

As mentioned in the introduction, there are some differences in the scope and format of the guidelines. The GOLD guideline differs from the other two guidelines in its global perspective and in its emphasis on prevention strategies. This guideline presents a COPD management plan with four components: (1) assessment and monitoring of disease, (2) reduction of risk factors, (3) management of stable COPD, and (4) management of exacerbations. The GOLD, NCCCC/NICE and SMOH guidelines also differ from the FMS guideline by including

recommendations for pulmonary rehabilitation which are addressed in Part III of this synthesis (currently under development).

Areas of Agreement

Definition of COPD

The three guidelines generally agree on the definition of COPD. Specifically, they agree that the disease is characterized by airflow limitation or obstruction, and that COPD is a progressive disease that is not fully reversible. A change made by GOLD in its 2006 guideline was to incorporate the phrase "preventable and treatable" following the ATS/ERS (American Thoracic Society/European Respiratory Society) recommendations to recognize the need to present a positive outlook for patients, to encourage the health care community to take a more active role in developing programs for COPD prevention, and to stimulate effective management programs to treat those with the disease.

Differential Diagnosis

All four guidelines note that the primary differential diagnosis for COPD is asthma.

Physical Examination

The four guidelines generally agree that physical examination is rarely diagnostic in COPD.

Spirometry

The four guidelines agree on the importance of early spirometry to assess airflow limitation and aid in diagnosis of COPD.

Assessing Severity of Disease

The guidelines each recommend staging systems based on FEV_1 values for degree of severity (although the values and classification schemes vary among guidelines). All guidelines generally agree that the purpose for assessing severity is for prognostic and/or therapeutic purposes. In addition, all four guidelines remark on the importance of considering other factors (i.e., signs, symptoms, complications) in addition to FEV_1 values in assessing severity of disease. GOLD points out that the FEV_1 cutpoints are used for the purposes of simplicity and are not clinically validated and may overestimate the prevalence of COPD in some groups, such as the elderly. Similarly, NCCCC/NICE cautions against use of spirometry alone to classify severity of the disease because the results may underestimate the impact of the disease in some patients and overestimate it in others.

Chest X-ray

All of the guidelines agree that chest x-ray is of limited value in the diagnosis of COPD. However, GOLD, NCCCC/NICE and SMOH recommend chest x-ray to exclude alternative diagnoses.

Measurement of Arterial Blood Gases (ABG)/Oximetry

All of the guidelines agree that blood gas analysis is an appropriate investigation for advanced COPD.

Measurement of Alpha-1 Antitrypsin (AAT) Levels

GOLD and NCCCC/NICE recommend measurement of AAT levels in patients with early onset COPD and a family history. GOLD makes this recommendation for patients of Caucasian descent; NCCCC/NICE does not specify. The FMS and SMOH guidelines do not specifically recommend testing for AAT level, but FMS notes that deficiency of AAT is a rare cause of emphysema in young patients and SMOH similarly states that severe hereditary deficiency of AAT is a well-documented host factor, although rare locally.

Overall Management Strategy and General Approach to Pharmacologic Therapy

The guidelines are in general agreement that a stepped approach to treatment should be used, with therapy based on severity of symptoms and coexisting conditions.

Bronchodilators

All of the guidelines generally agree on the use and efficacy of various types of bronchodilating drugs. Short-acting or long-acting $beta_2$-agonists and anticholinergics, alone or in combination, are recommended for symptom control.

There is general agreement that short-acting bronchodilators, including short-acting $beta_2$- agonists, are appropriate as an initial treatment for relief of symptoms.

All guidelines agree that methylxanthines should not be used routinely or as a first line treatment. Caution is advised due to the potential toxicity of the drugs.

Corticosteroids

All of the guidelines generally agree that corticosteroids have limited or no long-term positive effect on lung function. All four recommend use of inhaled corticosteroids in qualifying patients in order to reduce frequency of exacerbations and improve health status or slow the decline in health status.

Vaccines

All of the guidelines recommend influenza vaccination in COPD patients. NCCCC/NICE recommends pneumococcal vaccination, while FMS states that it may be beneficial. GOLD recommends the pneumococcal vaccine in COPD patients 65 years and older. SMOH states that pneumococcal vaccination may be considered in COPD patients, and if considered, usually only one dose of the vaccine is needed. A second dose is recommended for persons aged 65 or older who received their first dose when they were under 65, if 5 or more years have passed.

Alpha-1 Antitrypsin Augmentation Therapy

While FMS and SMOH do not offer recommendations regarding this therapy, GOLD and NCCCC/NICE generally agree that the therapy may be appropriate for qualifying individuals.

Antibiotics

All four guidelines are in agreement that prophylactic antibiotic therapy cannot be recommended for the management of stable COPD.

Mucolytic Therapy

There is general agreement that mucolytic therapy, while not used routinely, is appropriate at times in stable COPD patients. FMS recommends only temporary use. GOLD states that a few patients with viscous sputum may benefit, but that the overall benefits are low. According to NCCCC/NICE, mucolytic therapy should be considered in patients with a chronic cough productive of sputum and should be continued if there is a symptomatic improvement. SMOH states that there is no evidence to date to support the benefit of the routine use of mucolytics in stable COPD. For differences, see Areas of Differences.

Antitussives

GOLD and NCCCC/NICE both agree that antitussive therapy should not be used in the management of stable COPD. FMS and SMOH do not offer recommendations.

Long-term Oxygen Therapy (LTOT)

All guidelines generally agree that LTOT should be considered in qualifying individuals, particularly individuals in advanced stages of COPD, in order to preserve vital organ function and extend life.

Smoking Cessation

All guidelines agree on the importance of promoting smoking cessation to prevent and/or slow down the progression of COPD.

Patient Education

GOLD, NCCCC/NICE and SMOH agree that patient education is beneficial as part of a COPD management program to help patients cope with their illness as well as to meet specific objectives, such as education in smoking cessation. NCCCC/NICE cautions against using programs designed for asthma with COPD patients. FMS does not address patient education.

Surgery

All of the guidelines generally agree that surgery may be appropriate management of COPD in qualifying individuals, and all address bullectomy, lung transplant and lung volume reduction surgery (LVRS) as possible surgical options.

Areas of Differences

Physical Examination

Although there is general agreement among guidelines that physical examination is rarely diagnostic in COPD, GOLD emphasizes the importance of physical examination as a part of patient care and offers detailed recommendations (e.g., inspection, palpation and percussion, and auscultation). FMS also describes physical symptoms suggestive of severe COPD but notes that their absence does not exclude mild COPD. NCCCC/NICE offers no specific recommendations for physical examinations. They generally emphasize that diagnosis is suspected based on signs and symptoms that are supported by spirometry.

Assessing Severity of Disease

While all of the guidelines recommend a staging system based on FEV_1 values, the actual defining values and categories vary. For instance, the FMS guideline distinguishes between two different stages of disease (mild disease and continuous symptoms). NCCCC/NICE describes a three-stage system (mild, moderate, and severe). GOLD describes a four-stage system (mild, moderate, severe, and very severe) and SMOH the five-stage system previously employed by GOLD.

GOLD points out that their staging system "should only be regarded as an educational tool, and a very general indication of the approach to management." It was not clinically validated. (See the classification scheme for each group Table below)

All four guidelines classify the severity of COPD based on airflow limitation as measured by spirometry. In previous versions of its guideline, GOLD identified an early stage of COPD (*Stage 0*), in which a person has chronic symptoms of COPD but normal spirometry. With the release of the 2006 guideline they have modified the spirometric classification to no longer include *Stage 0*, as there is incomplete evidence that individuals who meet the definition of "At Risk" (chronic cough and sputum production, normal spirometry) necessarily progress on to *Stage I*. The SMOH guideline, however, though also released in 2006, relies on the previous GOLD classification scheme and therefore includes the *Stage 0* category.

Assessing Severity of COPD Disease

FMS (2007)
Mild disease: • Patients with occasional symptoms (generally FEV_1 >50% predicted)

Continuous symptoms

- Patients with continuous symptoms (generally FEV_1 <50% predicted)

GOLD (2007)

Stage I [Mild COPD]:

- $FEV_1/FVC < 0.70$
- $FEV_1 \geq 80\%$ predicted

Stage II [Moderate COPD]:

- $FEV_1/FVC < 0.70$
- $50\% \leq FEV_1 < 80\%$ predicted

Stage III [Moderate COPD]:

- $FEV_1/FVC < 0.70$
- $30\% \leq FEV_1 < 50\%$ predicted

Stage IV [Very Severe COPD]

- $FEV_1/FVC < 0.70$
- FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure

NCCCC/NICE (2004)

Mild airflow obstruction:

- 50 to 80% predicted FEV_1

Moderate airflow obstruction:

- 30 to 49% predicted FEV_1

Severe airflow obstruction:

- <30% predicted FEV_1

SMOH (2006)

Stage 0 [At Risk]:

- Normal spirometry

- Chronic symptoms (cough, sputum production)

Stage I [Mild COPD]:

- $FEV_1/FVC < 70\%$
- $FEV_1 \geq 80\%$ predicted
- With or without chronic symptoms (cough, sputum production)

Stage II [Moderate COPD]:

- $FEV_1/FVC < 70\%$
- $50\% \leq FEV_1 < 80\%$ predicted
- With or without chronic symptoms (cough, sputum production)

Stage III [Moderate COPD]:

- $FEV_1/FVC < 70\%$
- $30\% \leq FEV_1 < 50\%$ predicted
- With or without chronic symptoms (cough, sputum production)

Stage IV [Very Severe COPD]

- $FEV_1/FVC < 70\%$
- $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

Instead of classifying severity of disease, NCCCC/NICE classifies severity of airflow obstruction, which they point out can be used to guide therapy and predict prognosis. Unlike FMS or GOLD, NCCCC/NICE recommends evaluation of BMI and exercise capacity in assessing severity, stating that results reflect the impact of the disease in an individual and predict prognosis.

Bronchodilator Reversibility Testing

There is some disagreement among guidelines on the indications for reversibility testing. GOLD states that neither bronchodilator nor oral glucocorticosteroid reversibility testing predicts disease progression, whether judged by decline in FEV_1, deterioration of health status, or frequency of exacerbations in patients with a clinical diagnosis of COPD and abnormal spirometry. They add, however, that in some cases (e.g., a patient with an atypical history such as asthma in childhood and regular night waking with cough or wheeze) a bronchodilator and/or glucocorticosteroid reversibility test may be indicated. They suggest a possible protocol for doing so. FMS recommends testing with a bronchodilating drug at diagnosis and subsequent assessment of response, and as a component of the differential diagnosis for asthma. SMOH similarly recommends that bronchodilator reversibility testing be performed to help identify some subjects with asthma or a large asthma component to COPD and to establish a patient's best attainable lung

function. In contrast, NCCCC/NICE does not consider reversibility testing necessary or helpful for initial diagnostic process to plan initial therapy with bronchodilators or corticosteroids. They argue that results of testing may be unhelpful or misleading; asthma should be differentiated from COPD by features at the history and examination and longitudinal observations. Reversibility testing should be reserved to resolve diagnostic doubt.

Theophylline

There is some disagreement about the efficacy of methylxanthines. Citing a 2004 Cochrane review, FMS note that theophylline has a modest effect on FEV_1 and FVC and slightly improves arterial blood gas tensions in moderate to severe COPD. In contrast, GOLD states theophylline is effective in COPD (but not a preferred treatment due to toxicity). NCCCC/NICE reports that theophylline is effective in combination with $beta_2$-agonists or anticholinergics. SMOH notes that theophylline may be a useful addition where symptom control is still not achieved with existing inhaled bronchodilator therapy. In spite of possible efficacy, they all agree about proceeding with caution.

Mucolytic Therapy

While all guidelines generally agree that mucolytic therapy is appropriate at times, there is some disagreement. For instance, FMS states that any use should be temporary. On the other hand, NCCCC/NICE recommends ongoing mucolytic therapy in patients with a chronic cough productive of sputum who have received symptomatic improvement from the mucolytic therapy. NCCCC/NICE bases the recommendations on evidence of benefit. SMOH states there is no evidence to date to support the benefit of the routine use of mucolytics.

Antioxidant Agent

Although FMS does not comment on the role of antioxidants, GOLD and NCCCC/NICE differ in perspectives. NCCCC/NICE recommends against the use of the antioxidant supplements alpha-tocopherol and beta-carotene, alone or in combination. GOLD states that antioxidants, in particular N-acetylcysteine, have been shown to reduce the frequency of exacerbations, leading to speculations that it could have a role in the treatment of patients with recurrent exacerbations. SMOH states that there is no evidence to date to support the benefit of the routine use of anti-oxidants.

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