

VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF OUTPATIENT CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)



Guideline Summary



Key Elements Addressed By the Guideline

1. Consider the diagnosis of COPD in all smokers and ex-smokers over the age of 45; cigarette smoking accounts for about 85 percent of the risk of developing COPD.
2. Smoking cessation is the single most effective way to reduce the risk of developing COPD and slow the rate of decline in lung function compared to that of non-smokers.
3. The diagnosis of COPD rests on the clinical history and on the requirement that spirometry demonstrates an airflow limitation that is not fully reversible.
4. Spirometry is the most reproducible, standardized, and objective way of measuring airflow limitation and is closely associated with prognosis.
5. Airflow limitation that is not fully reversible is defined as being present when the postbronchodilator values for the ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) (FEV1/FVC) is below 0.70
6. Severity of COPD is based on the level of airflow limitation; tailored therapy for COPD is based on the severity of symptoms and functional limitation.
7. Breathlessness and functional limitation can be rated numerically with the simple Modified Medical Research Council (MMRC) dyspnea scale.
8. Step-Care for bronchodilators:
 - Inhaled bronchodilators provide symptom relief
 - Long-acting bronchodilators provide sustained relief of symptoms in moderate to very severe COPD
 - Combination therapy is useful in moderate and very severe COPD
 - Adding inhaled glucocorticoids to optimize bronchodilator therapy reduces exacerbations in patients with both severe COPD (FEV1 < 50 percent predicted) and frequent exacerbations (> one/year); long-term use of oral glucocorticoids is not recommended
9. Pulmonary rehabilitation reduces dyspnea, anxiety, and depression; improves exercise capacity and quality of life (QOL); and may reduce hospitalizations
 - Exercise alone or as part of a comprehensive rehabilitation program improves symptoms, self-confidence, endurance, and QOL.
10. Long-term oxygen for more than 15 hours/day prolongs life in hypoxemic patients with PaO₂ of 55 mm Hg or less.
11. Diagnostic sleep tests should be considered if patients with COPD have pulmonary hypertension, hypercapnia, and daytime somnolence or witnessed apneas.
12. End-of-life care in patients with end-stage COPD may be considered.



STRENGTH OF RECOMMENDATION RATINGS

A	A strong recommendation that the clinicians provide the intervention to eligible patients. <i>Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.</i>
B	A recommendation that clinicians provide (the service) to eligible patients. <i>At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.</i>
C	No recommendation for or against the routine provision of the intervention is made. <i>At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.</i>
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. <i>At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.</i>
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. <i>Evidence that the intervention is effective is lacking, or poor quality, or conflicting and the balance of benefits and harms cannot be determined.</i>

Definitions*

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterized by expiratory airflow limitation that is not fully reversible. The expiratory airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.

Chronic bronchitis is defined clinically as a chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded.

Emphysema is defined pathologically as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.

Asthma is characterized by variable airflow obstruction and differs from COPD in its pathogenic and therapeutic response, and should therefore be considered a different clinical entity. (See the VA/DoD Clinical Practice Guideline for the Management of Asthma.) The high prevalence of asthma and COPD in the general population results in the coexistence of both disease entities in many individuals.

Other conditions: poorly reversible airflow limitation associated with bronchiectasis, cystic fibrosis, and fibrosis due to tuberculosis are not included in the definition of COPD but should be considered in its differential diagnosis.

**Source: American Thoracic Society (ATS)/European Respiratory Society (ERS) in Standards for the Diagnosis and Management of Patients with COPD (ATS/ERS, 2004). www.thoracic.org/copd; Similar definitions may be found in the British Thoracic Society, 1997 and The Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2005 [www.goldcopd.org].*

CASE FINDING OF COPD

The diagnosis of COPD should be suspected in any patient who has a history of tobacco use (smoking) and any of the following [C]:

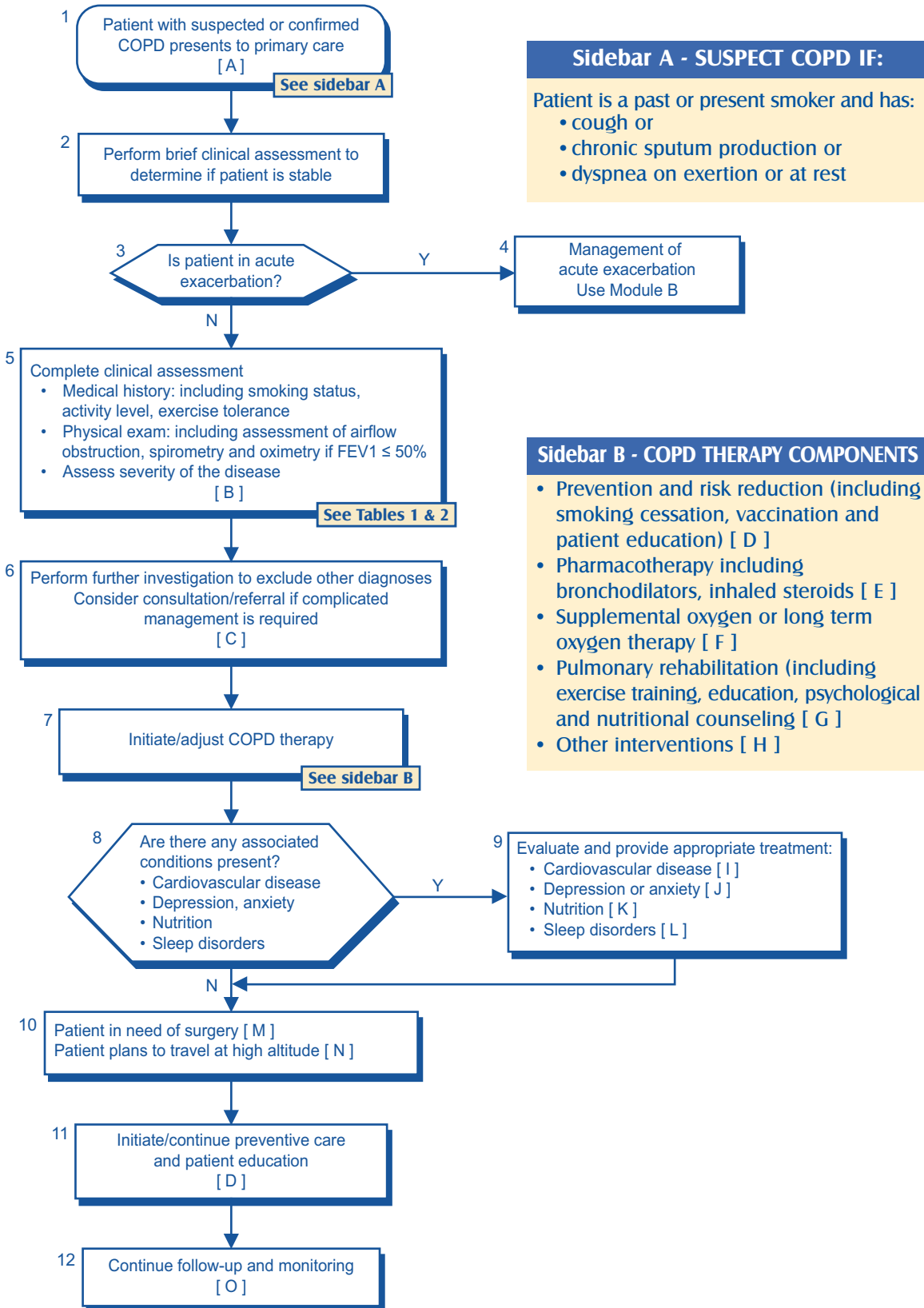
- Chronic cough, or
- Chronic sputum production, or
- Dyspnea on exertion or rest

The diagnosis of COPD must be confirmed by spirometry. [I]

VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF COPD

Module A: Management of COPD

A



MODULE A: MANAGEMENT OF COPD

ACTION STATEMENTS AND RECOMMENDATIONS

SCREENING

Annotation A: Patient with Suspected or Confirmed COPD Presents to Primary Care

1. Persons with a history of smoking and the presence of cough or chronic sputum production or dyspnea should be assessed for COPD with spirometry. [C]

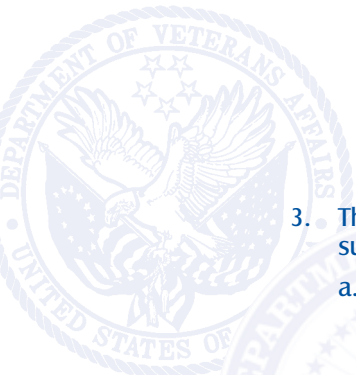
CLINICAL ASSESSMENT

Annotation B: Clinical Assessment

HISTORY AND PHYSICAL EXAMINATION

All patients with known or suspected COPD should have a focused history and physical examination to assess for the presence of airflow limitation. [I]

2. The following core elements of the medical history should be evaluated in patients with suspected or proven COPD [I]:
 - a. *Shortness of breath* – patients should quantify their level of dyspnea (resting vs. exertional). Early in the disease course, patients often complain of exertional dyspnea. As the disease progresses, exercise tolerance worsens and patients may develop resting dyspnea.
 - b. *Cough* – duration and character of the cough should be quantified. The presence of a productive cough is a second clinical hallmark of COPD. This cough is typically initially worse in the morning, but can be present throughout the day. An isolated nocturnal cough is typically not characteristic of COPD. Chronic bronchitis is defined by the presence of a persistent cough for at least 3 months for 2 or more consecutive years.
 - c. *Sputum production* – volume (amount) and character (color, thickness) of sputum production should be qualified. Sputum production is required for a diagnosis of chronic bronchitis.
 - d. *Risk factor assessment* – tobacco use, particularly cigarette smoking, is the primary risk factor for developing COPD. Use should be quantified in pack-years (number of packs per day x number of years = pack-years). A 10-pack year history of smoking is considered to be the threshold for development of COPD. There is no comparable standard for pipes or cigars that may also produce COPD. Environmental pollutant exposure and occupational exposure to vapors, fumes, or irritants are important secondary risk factors.
 - e. *Other important elements in the initial evaluation of COPD:*
 - Prior medical history of asthma, allergies, or recurrent respiratory illnesses (particularly in childhood)
 - Family history of COPD
 - Self-reported history of prior COPD exacerbations and/or hospitalizations
 - Presence of comorbid conditions, in particular coronary artery disease, congestive heart failure, depression, and anxiety.
3. The following core elements of the physical examination should be evaluated in patients with suspected or proven COPD [I]:
 - a. *Vital signs* – for patients with COPD, an assessment of pulse oximetry and body mass index (BMI = kg/m²) should be included with the vital signs.



- b. *Inspection* – clinical observation should be performed to assess for the following elements:
 - Chest wall morphology (e.g., ‘barrel-chest’); use of accessory muscles (e.g., ‘suprasternal retractions’); pursed-lip breathing (surrogates that suggest airflow limitation); and tracheal tug (sign of hyperinflation)
 - Forced Expiratory Time – patients should be asked to completely empty their lungs following a maximal inspiratory effort
 - Central cyanosis (a surrogate for oxygen saturation); oxygen desaturation may be present in the absence of cyanosis; cyanosis is indicative of severe desaturation
 - Miscellaneous signs – jugular venous distension suggests elevated right heart pressures; bilateral peripheral edema may suggest cor pulmonale.
- c. *Palpation/Percussion* – these elements are often unhelpful in patients with COPD, but may be helpful in diagnosing pulmonary hyperinflation.
- d. *Auscultation* – the following elements should be noted on the cardiopulmonary examination:
 - Breath sounds are often diminished or distant in patients with COPD,
 - A widened split second heart sound is suggestive of cor pulmonale.

SPIROMETRY AND REVERSIBILITY FOR DIAGNOSIS

Spirometry should be obtained in all stable patients suspected of or having a diagnosis of COPD. [B]

- 4. Spirometry should be performed and documented in the medical record. [B]
- 5. A diagnosis of expiratory airflow limitation can be made if the post-bronchodilator FEV1/FVC or FEV1/VC ratio is 0.70 or less. Where possible, value should be compared to age-related normal values to avoid over diagnosis of COPD in the elderly. [I]
- 6. Reversibility should not be used to predict response to treatment or to distinguish between COPD and asthma. [B]
- 7. Spirometry should be repeated if there is a clinically significant unexplained change in respiratory symptoms. [I]
- 8. All patients presenting with airflow limitation at a relative early age (of the fourth to fifth decade) or with a family history of COPD should be tested for alpha-1-antitrypsin deficiency. [I]
- 9. Oximetry should be considered in patients with COPD and should be performed in all patients with severe or very severe COPD (FEV1 < 50 percent predicted) to determine the degree of hypoxemia and the potential need for long-term oxygen therapy at rest and/or during exercise. [C]

ASSESSING SEVERITY OF THE DISEASE

COPD severity should be assessed on the basis of percentage of predicted FEV1 or degree of dyspnea related to activities. [I]

- 10. The forced expiratory volume in one second (FEV1) should be used to stratify disease severity by airflow limitation. [I] (See Table 1)
- 11. The Modified Medical Research Council (MMRC) Dyspnea Scale should be used to grade severity of breathlessness according to the level of exertion required to elicit it and help determine treatment. [C] (See Table 2)

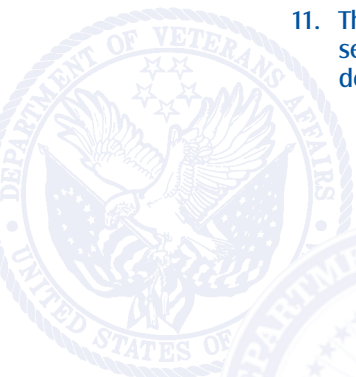


Table 1: Severity of COPD Based on Spirometry (adopted from ATS/ERS, 2004)

Stage	Severity	Postbronchodilator FEV1/FVC	FEV1 % predicted
0	At-Risk ⁽¹⁾	≥ 0.7	≥ 80
1	Mild	≤ 0.7	≥ 80
2	Moderate	≤ 0.7	50 – 79.9
3	Severe	≤ 0.7	30 – 49.9
4	Very Severe	≤ 0.7	< 30

⁽¹⁾ Patients who smoke or are exposed to pollutants; and have cough, sputum or dyspnea; or have family history of respiratory disease. (There is insufficient evidence to support this category.)

FEV1: forced expiratory volume in one second; FVC: forced vital capacity

Table 2: Severity of COPD Based on Dyspnea⁽¹⁾

Severity	Score	Degree of Breathlessness Related to Activities
None	0	Not troubled with breathlessness except with strenuous exercise
Mild	1	Troubled by shortness of breath when hurrying or walking up a slight hill
Moderate	2	Walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on the level
Severe	3	Stops for breath after walking approximately 100 meters or after a few minutes on the level
Very Severe	4	Too breathless to leave the house or breathless when dressing or undressing

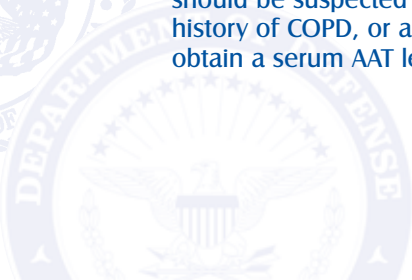
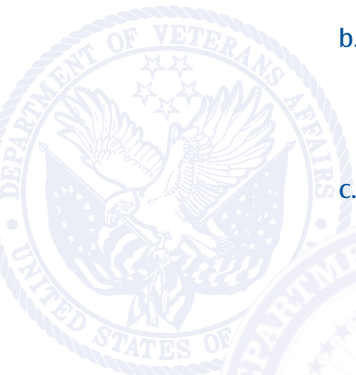
(1) Modified Medical Research Council (MMRC) Dyspnea Scale (Bestall et al., 1999)

Annotation C: Further Investigation to Exclude Other Diagnoses

DIAGNOSTIC WORKUP

Other investigations, in addition to spirometry, may be necessary as clinically indicated. [I]

12. A diagnosis of COPD requires objective evidence of airflow obstruction via pre- and postbronchodilator spirometry. [B]
13. A chest X-ray should be considered to rule out other diagnoses and for later use as a baseline. A chest X-ray is not sensitive for the diagnosis of COPD. [C]
14. Other investigations may be necessary as clinically indicated [I]:
 - a. *Computed tomography (CT)* – can exclude other diseases and define bullae and is essential to identify patients eligible for lung volume reduction surgery
 - b. *Oximetry* – should be considered in patients with COPD and should be performed in all patients with severe or very severe COPD (FEV1 < 50 percent predicted) to determine the degree of hypoxemia and the potential need for long-term oxygen therapy at rest and/or during exercise. Nocturnal pulse oximetry should be performed in patients considered solely for nocturnal oxygen supplementation.
 - c. *Alpha1-antitrypsin (AAT)* – AAT deficiency accounts for less than one percent of COPD. It should be suspected if there is early onset of COPD, little or no history of smoking, a family history of COPD, or a predominance of basilar emphysema. If AAT deficiency is suspected, obtain a serum AAT level.



- d. *Arterial blood gases* – arterial blood gases should be done in patients with very severe COPD (FEV1 < 30 percent predicted); signs of right heart failure (cor pulmonale); polycythemia (hematocrit > 55 percent); or respiratory failure. Blood gases are an alternative to pulse oximetry in patients being considered for O₂ supplementation. Pulse oximetry can determine arterial oxygen saturation, but pulse oximetry does not yield PCO₂.
- e. *Full pulmonary function tests* – lung volumes, carbon monoxide diffusing capacity and flow-volume loops are not required for routine assessment but can provide additional information useful for resolving diagnostic uncertainty and/or assessing surgical risk. A reduced carbon monoxide diffusion capacity may suggest the presence of emphysema.
- f. *Exercise testing* – exercise testing may be of value in patients with a disproportionate degree of dyspnea for their FEV1. Exercise testing can quantify impairment and/or disability and help to select patients able to safely undergo lung resection.
- g. *ECG* – to assess cardiac status if pulmonary or nonpulmonary heart disease is suspected or present.
- h. *Echocardiogram* – to assess right and left cardiac status if cardiac dysfunction or disease is suspected or present.
- i. *Sputum cultures* – consider in patients with persistently purulent sputum or during recurrent infectious exacerbations.
- j. *Complete blood count test* should be done if anemia or polycythemia is suspected.

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 (See Box 1: Clinical Features Differentiating COPD & Asthma).

REFERRAL TO PULMONARY CONSULTANT

Patients with severe COPD or comorbidity that requires complicated management should be referred to a pulmonary subspecialist. [I]

15. Patients with COPD should be referred for consultative opinion if they request it, if there is diagnostic uncertainty, if the disease is very severe or complicated, or if the primary care provider chooses so. [I]

Box 1: Clinical Features Differentiating COPD & Asthma

Clinical Features	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptoms under age 35	Rare	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Night time waking with breathlessness and or wheeze	Uncommon	Common
Commonly associated with atopic symptoms and seasonal allergies	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common
Favorable response to inhaled glucocorticoids	Inconsistent	Consistent

Annotation D: Prevention and Risk Reduction

PATIENT EDUCATION

16. Patient should be educated about the disease, cause, therapy, and complications of COPD. [I]

SMOKING CESSATION

All patients must be screened for tobacco use and encouraged to stop smoking at every visit, as smoking cessation is the only known intervention to reduce the decline in FEV1. [A]

17. All patients should be counseled not to smoke and to avoid secondhand smoke. [A]
 18. All smokers must be told that they need to quit smoking. [A]
 19. All smokers should be assessed for willingness to quit. [C]
 20. All smokers should be counseled on smoking cessation and be considered for medications that assist in smoking cessation. [A] (See Table 3, Table 4)

*For detailed recommendations and evidence refer to the *VA/DoD Clinical Practice Guideline for Management of Tobacco Use*.

VACCINATION

Provide an annual influenza vaccine to individuals with COPD. [A]

Provide a pneumococcal polysaccharide vaccine to individuals with COPD. [B]

21. An annual influenza vaccination is recommended for individuals with COPD unless contraindicated due to severe anaphylactic hypersensitivity to egg protein. The optimal time to receive influenza vaccine is October - November. [A]
 22. Although insufficient data exist for use of pneumococcal vaccination in individuals with COPD, data from elderly populations with or without chronic disease provides supportive evidence for its use. [A]
 23. Pneumococcal vaccines are routinely given as a one-time dose (administer if previous vaccination history is unknown). One-time revaccinations are recommended 5 years later for people at the highest risk for fatal pneumococcal infection and for people older than 65 years if the first dose was given prior to the age of 65 and more than 5 years have elapsed since the previous dose. [I]

Table 3: Suggested Strategies to Promote Smoking Cessation: "5 A's"

Strategy 1:	Ask: Systematically identify all tobacco users at every visit. Implement an office wide system that ensures that for every patient at every clinic visit, tobacco use status is queried and documented.
Strategy 2:	Advise: Strongly urge all smokers to quit. In a clear, strong, and personalized manner, urge every smoker to quit.
Strategy 3:	Assess: Assess smokers willingness to make a quit attempt. Ask every smoker if he or she is willing to make a quit attempt at this time.
Strategy 4:	Assist: Aid the patient in quitting. Help patient develop a quit plan, encourage nicotine replacement therapy or bupropion except in special circumstances, give key advice on successful quitting, and provide supplementary materials.
Strategy 5:	Arrange: Schedule follow-up contact either in person or via telephone.

* VA/DoD Clinical Practice Guideline for Management of Tobacco Use

Table 4: Motivational Intervention to Promote Smoking Cessation: "5 R's"*

Relevance:	Encourage patient to indicate why quitting is personally relevant.
Risks:	Ask the patient to identify potential negative consequences of tobacco use.
Rewards:	Ask the patient to identify potential benefits of stopping tobacco use.
Roadblocks:	Ask the patient to identify barriers or impediments to quitting.
Repetition:	The motivational intervention should be repeated every time an unmotivated patient has an interaction with a provider. Tobacco users who have failed in previous attempts should be told that most people make repeated quit attempts before they are successful.

* VA/DoD Clinical Practice Guideline for Management of Tobacco Use

THERAPY INTERVENTIONS FOR COPD

Annotation E: Pharmacotherapy Including Bronchodilators and Inhaled Glucocorticoids

PHARMACOTHERAPY OF COPD

See Module C: Pharmacotherapy for specific recommendations (See Table 5, Table 6, Figure 2). For dosage of selected COPD drug therapy (See Table C- 1-6)

Table 5: Key Points for COPD Step-Care Therapy

Pharmacotherapy for patients with COPD is based on a step-up approach:

1. Therapy to address symptoms should make use of non-pharmacologic intervention to improve outcomes (i.e., smoking cessation, education, rehabilitation, and pulmonary rehabilitation).
2. Pharmacotherapy should balance overall efficacy which includes acceptance and adherence against risks for adverse effects (toxicity).
3. Patient symptomatic responses such as dyspnea, as well as a reduction in exacerbations, should be the primary basis for determining response to therapy.
4. Continue ongoing evaluation of the patient's response to therapy and progression of disease.
5. As COPD progresses, additional pharmacotherapy is usually needed.
6. Patient's preference should be considered to improve acceptance and adherence to therapy.
7. Patients with severe airflow limitation (FEV1 < 50 percent predicted) and minimal symptoms should be considered for a trial of pharmacologic therapy.
8. COPD severity based on symptoms and FEV1 should always be documented initially and reassessed periodically based primarily on symptomatic progression of COPD.
9. The Modified Medical Research Council (MMRC) scale of dyspnea, in addition to clinical assessment, is indicated to grade symptom severity.
10. Treatment is predominantly based on symptoms and a suggested steppedup approach is recommended (see Table 6).

Table 6: Step-Care Pharmacotherapy in COPD

Step	Symptoms ①	Maintenance Therapy ②	Rescue therapy	Other Interventions
A	Asymptomatic	No medication indicated	--	Smoking cessation; influenza, and other vaccinations
B	Symptoms less than daily	No scheduled medication indicated	SABA ⑥	Smoking cessation; influenza, and other vaccinations
C	Symptoms not controlled with rescue therapy or daily symptoms	Scheduled SAAC OR Combination SABA + SAAC ③	SABA ⑥	Smoking cessation; influenza, and other vaccinations
D	Symptoms not controlled ②	Combination SAAC + LABA OR LAAC ④	SABA ⑥	Smoking cessation; influenza, and other vaccinations Consider Pulmonary Rehabilitation ⑦
E	Symptoms not controlled ②	Combination LABA + LAAC ④	SABA ⑥	Smoking cessation; influenza, and other vaccinations Refer to Pulmonary Rehabilitation ⑦
F	Exacerbations of more than one per year and severe disease (FEV1 < 50%)	Consider adding an inhaled glucocorticoid ⑤	SABA ⑥	Smoking cessation; influenza, and other vaccinations Refer to Pulmonary Rehabilitation ⑦

SAAC – Short-acting anticholinergic; SABA – Short-acting beta-agonist; LABA – Long-acting inhaled beta-agonist; LAAC – Long-acting anticholinergic

- ① **Spirometry** is essential to confirm the presence of airflow obstruction (low FEV1 and FEV1/VC ratio). Base therapy on symptoms, but consider alternate diagnoses (heart disease, pulmonary emboli, etc.) if out of proportion to spirometry.
- ② Use the lowest level of therapy that satisfactorily relieves symptoms and maximizes activity level. Assure compliance and proper use of medications before escalating therapy. It is unusual for patients with COPD with FEV1 above 70% to require therapy beyond short-acting bronchodilators; if these patients do not improve they should be considered for alternative diagnoses.
- ③ Consider use of **inhaler** containing both a short-acting beta 2-agonist and an anticholinergic. Nighttime symptoms are frequently better controlled with a long-acting inhaled beta 2-agonist.
- ④ Consider adding a **theophylline trial** (slow release theophylline adjusted to the level of 5 to 12 µg/ml) with caution due to adverse effects. Nighttime respiratory symptoms are frequently controlled, but theophylline may lead to insomnia. Discontinue if a benefit is not evident within several weeks.
- ⑤ Consider high dose **inhaled glucocorticoids** in patients with severe COPD (FEV1 < 50 % predicted) and at least one exacerbation in the prior year. A combination of a high dose inhaled glucocorticoid and a long-acting beta 2-agonist may help provide long-term maintenance for symptomatic COPD and improve quality of life (QOL). The use of oral glucocorticoids for maintenance therapy is discouraged.
- ⑥ Short-acting inhaled beta 2-agonists (less than 12 puffs/day) may continue to be used as needed. Inhaled long-acting beta 2-agonists should not be used as rescue therapy.
- ⑦ **Pulmonary rehabilitation** should be offered to patients who, despite optimal medical therapy, have reduced exercise tolerance and/or dyspnea limiting exercise.

Figure 2. Step-Care Pharmacotherapy in COPD

A	Reduce risk factor(s): smoking cessation; influenza and other vaccinations
B	SABA when needed
C	Scheduled SAAC OR Combination SAAC + SAAB + SABA when needed*
D	Combination SAAC + LABA OR LAAC + SABA when needed*
E	LABA + LAAC + SABA when needed *
F	Add inhaled glucocorticoids if repeated exacerbations and FEV1 < 50%

* Theophylline may be added at each step with caution regarding adverse effects.

SAAC – Short-acting anticholinergic; SABA – Short-acting beta-agonist; LABA – Long-acting inhaled beta-agonist; LAAC – Long-acting anticholinergic

Annotation F: Supplemental and Long-term Oxygen Therapy

OXYGEN THERAPY

Patients with COPD should be periodically evaluated for the need of supplemental oxygen. Supplemental oxygen for those exhibiting signs of tissue hypoxia may increase survival of patients with severe COPD. Oxygen may also be used for exertional hypoxemia or nocturnal hypoxemia.

24. Oximetry should be considered in patients with COPD and should be performed in all patients with severe or very severe COPD (FEV1 < 50 percent predicted). [I]
25. Evaluation of nocturnal desaturation should be considered in patients with severe or very severe COPD (FEV1 < 50 percent predicted) who exhibit unexplained findings indicating nocturnal hypoxemia (e.g., polycythemia, pulmonary hypertension, and nocturnal restlessness). [I]
26. Oxygen therapy should be initiated in patients who have hypoxemia (PaO₂ ≤ 55 mm Hg and/or SaO₂ ≤ 88 percent). [A]
27. Oxygen therapy should be initiated in patients who have hypoxemia (PaO₂ of 56 to 59 mm Hg or SaO₂ ≤ 89 percent) and signs of tissue hypoxia such as hematocrit above 55, pulmonary hypertension, or cor pulmonale. [A]
28. Oxygen therapy should be provided during exercise in stable patients with COPD with exertional hypoxemia (SaO₂ ≤ 88 percent). [B]
29. Oxygen therapy should be provided for nocturnal hypoxemia (SaO₂ ≤ 88 percent). [I]
30. Patients who started to receive oxygen therapy while unstable or on suboptimal medical therapy should be reevaluated within one to 3 months for need of long-term oxygen therapy (LTOT). If repeated evaluation indicates a patient no longer qualifies for oxygen, cessation of oxygen should be considered. [B]
31. Patients who continue to receive long-term oxygen therapy (LTOT) should be reevaluated at least annually for continued need of LTOT. [I]
32. Patients prescribed oxygen should be cautioned about the potentially extreme fire hazard of smoking or lighting cigarettes in the presence of oxygen. [I]

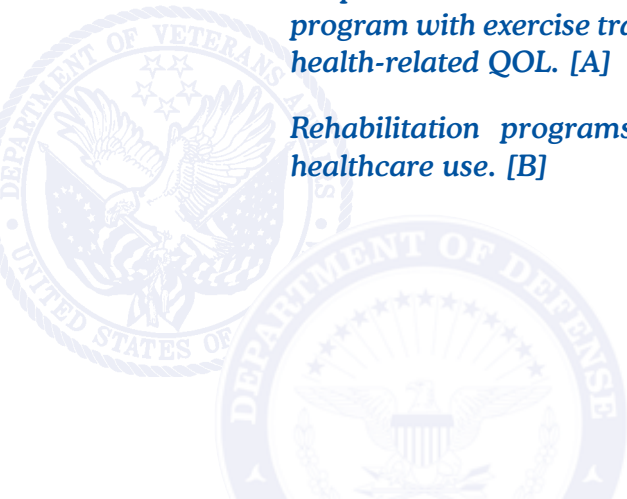
Annotation G Pulmonary Rehabilitation

PULMONARY REHABILITATION

Pulmonary rehabilitation should be offered to all patients with COPD who, despite optimal medical therapy, have reduced exercise tolerance and/or dyspnea limiting exercise. [A]

All patients with COPD with exertional symptoms should be offered a structured program with exercise training to reduce dyspnea and improve exercise tolerance and health-related QOL. [A]

Rehabilitation programs with education and self-management training reduce healthcare use. [B]



SELECTION OF PATIENTS

33. Pulmonary rehabilitation should be considered for patients with COPD who have dyspnea, reduced exercise tolerance, a restriction in activities, or impaired health status. [A]
34. Pulmonary rehabilitation should be offered to all patients who consider themselves disabled by COPD (Level 3 and above on the dyspnea scale). [B]
35. Pulmonary rehabilitation is recommended for patients with reduced exercise tolerance and restricted activities because of dyspnea. [A]

EXERCISE TRAINING

36. The exercise program should be supervised and should provide cardiovascular reconditioning with endurance and muscle strength training. [A]
37. The initial exercise program should be of sufficient length, duration, and frequency. [B]
38. Endurance training should be performed to improve physical endurance. [A]
39. Lower limb strength training should be performed to improve exercise tolerance (walking, cycling); upper extremity training improves arm strength. [B]
40. In order to maintain benefits, subsequent exercise training is needed. [B]
41. As studies show conflicting results, respiratory muscle training is not recommended to be part of a rehabilitation exercise program. [B]

EDUCATION AND SELF-MANAGEMENT

42. Patients with COPD with a prior hospitalization should be referred for pulmonary rehabilitation. [A]
43. Educational components and self-management programs should be included in rehabilitation programs, as it can reduce COPD exacerbations, hospital admission, and length of stay. [B]
44. Self-management programs should include the following [B]:
 - a. Skills training to optimally control the disease
 - b. Education about medications and devices and how to use them properly
 - c. Instruction on how to deal with exacerbations
 - d. Other aspects of coping with the disease.
45. The benefit of education, psychosocial support, and nutritional therapy as a single intervention, without exercise, are less well-documented. [I]

Annotation H: Other Interventions

MUCOLYTICS, ANTIOXIDANTS, AND ANTITUSSIVES

The use of mucolytics, antioxidants, or antitussive medications has little evidence of any effect on lung function. [D]

46. N-acetylcysteine (NAC) is not recommended for patients with COPD for the purpose of cough suppression. [D]
47. N-acetylcysteine (NAC) 600 mg by mouth every day may be considered to decrease the number of exacerbations in selected patients with COPD with primarily chronic bronchitis who are not on inhaled glucocorticoids. [B]
48. Antioxidants, such as alpha-tocopherol (contained in vitamin E preparations) or beta-carotene, should not be administered to patients with COPD, as they have no significant effect on phlegm, cough, or dyspnea. [D]
49. Antitussives are not indicated in stable COPD. [I]

ALPHA L-ANTITRYPSIN AUGMENTATION THERAPY

Patients with COPD due to confirmed or suspected alpha1-antitrypsin (AAT) deficiency should be referred to a pulmonary subspecialist. [C]

Alpha1-antitrypsin augmentation therapy should be considered in patients with severe hereditary alpha1-antitrypsin (AAT) deficiency and established emphysema. [C]

50. Patients with COPD due to alpha1-antitrypsin (AAT) deficiency should be provided the usual COPD therapy – smoking cessation, preventive vaccinations, bronchodilators, supplemental oxygen if indicated, and pulmonary rehabilitation. [I]
51. Patients with severe alpha1-antitrypsin (AAT) deficiency who have stopped smoking and with moderate to severe COPD (FEV1 30 to 60 percent predicted) should be considered for AAT augmentation therapy. Furthermore, benefits are not clear for those with FEV1 either below 30 percent or above 60 percent predicted. [C]
52. Augmentation therapy is not indicated for patients without emphysema. [D]

LUNG VOLUME REDUCTION SURGERY

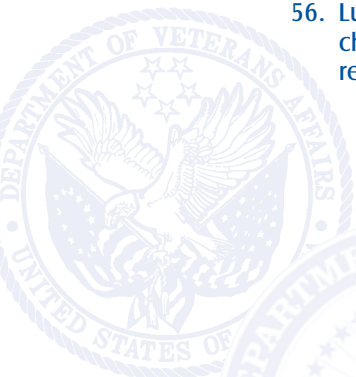
Consider lung volume reduction surgery (LVRS) in carefully selected patients with very severe COPD who comply with selection criteria that have been used in studies demonstrating benefit from LVRS. [A]

53. Referral for lung volume reduction surgery (LVRS) may be considered for patients with very severe COPD if they meet the following criteria [A]:
 - a. High-resolution computed tomography (CT) confirming bilateral emphysema
 - b. Total lung capacity before rehabilitation and after treatment with bronchodilators is greater than 100 percent predicted and residual volume is greater than 150 percent predicted
 - c. Post-bronchodilator FEV1 is less than 45 percent predicted
 - d. PaCO₂ less than 60 mm Hg, and PaO₂ greater than 45 mm Hg
 - e. Patient has completed a pulmonary rehabilitation program.
54. Lung volume reduction surgery (LVRS) should not be considered in patients whose FEV1 is less than 20 percent predicted and who either have homogenous emphysema or carbon monoxide diffusing capacity that is less than 20 percent or have non-upper lobe emphysema and high baseline exercise capacity. [D]
55. Lung volume reduction surgery (LVRS) should only be performed in medical centers with appropriately trained surgeons and availability of necessary equipment. [I]

LUNG TRANSPLANTATION

Consider lung transplantation as an option for carefully selected patients with very severe COPD who comply with selection criteria and have no contraindications. [C]

56. Lung transplantation may be considered in selected patients with advanced COPD. The choice of single lung transplantation (SLT) or bilateral lung transplantation (BLT) for COPD remains controversial. [C]



MANAGEMENT OF ASSOCIATED CONDITIONS

Annotation I: Evaluate and Provide Appropriate Treatment for Cardiovascular Disease

PULMONARY HYPERTENSION AND COR PULMONALE IN COPD

Patients with pulmonary hypertension and/or cor pulmonale should be referred to a specialist for the management of COPD and be provided long-term oxygen, if needed, and optimized. [A]

57. Patients with diagnosed or suspected cor pulmonale should be referred to a pulmonary subspecialist. [C]
58. Patients with pulmonary hypertension and/or cor pulmonale should be assessed for hypoxemia and provided long-term oxygen, if needed. [A]
59. Bronchodilators should be optimized and edema treated cautiously with diuretics. [C]
60. The management of cardiovascular diseases in patients with COPD should follow existing guidelines, including routine treatment with beta-blockers. [B]

Annotation J: Evaluate and Provide Appropriate Treatment for Depression or Anxiety Mental Health (Depression and Anxiety)

Healthcare providers should be alert to the possibility of presence of depression in patients with COPD and treat them according to depression guidelines.

61. Patients with COPD should be screened for depression and anxiety using validated screening and assessment tools. [B]
62. Patients diagnosed with depression or anxiety should be treated with pharmacotherapy and psychotherapy suitable for patients with COPD and the patient's age. [B]
63. Sedative anxiolytic for the treatment of anxiety should be avoided in patients with severe COPD. [D]

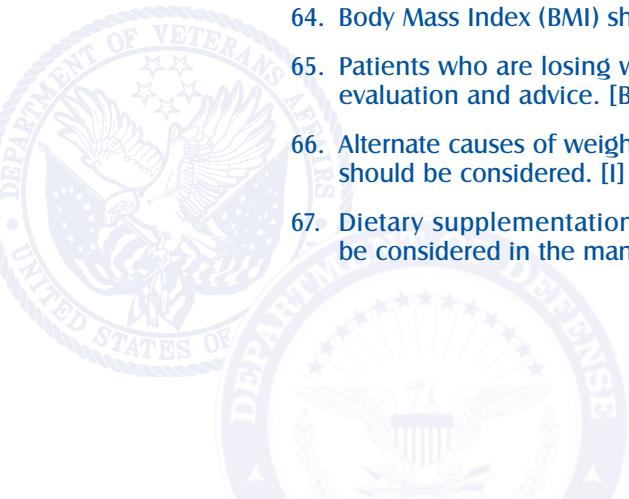
See the *VA/DoD Clinical Practice Guideline for Major Depressive Disorder*.

Annotation K: Evaluate and Provide Appropriate Treatment for Nutrition

MALNUTRITION

Malnutrition and weight loss in patients with COPD carry a poor prognosis and should be assessed and intervention considered.

64. Body Mass Index (BMI) should be monitored in patients with COPD. [B]
65. Patients who are losing weight over time ($BMI \leq 21 \text{ kg/m}^2$) should be referred for dietary evaluation and advice. [B]
66. Alternate causes of weight loss associated with COPD, such as lung cancer and lung infection, should be considered. [I]
67. Dietary supplementation in combination with exercise and nutritional consultation should be considered in the management of patients with COPD with weight loss or malnutrition. [B]



Annotation L: Evaluate and Provide Appropriate Treatment for Sleep Disorders

SLEEP DISORDERS IN PATIENTS WITH COPD

All patients with COPD should be questioned about symptoms of sleep disturbance and possible associated sleep apnea syndromes, such as snoring, witnessed apnea during sleep, and excessive daytime sleepiness.

68. Patients with COPD should be evaluated for sleep disorders by using medical interview, which should include standardized screening questionnaires for sleep disorders (e.g., insomnia, sleep apnea). [I]
69. Patients complaining of insomnia should be managed in outpatient primary care and may be treated with hypnotics cautiously. [I]
70. Patients with other sleep-related disorders (such as sleep apnea) should be referred to a sleep specialist. [I]

Annotation M: Special Considerations for a Patient in Need of Surgery

SPECIAL CONSIDERATIONS FOR A PATIENT IN NEED OF SURGERY

The preoperative evaluation of a patient with COPD depends upon the type and acuity of surgery and the severity of COPD.

EMERGENCY SURGERY

71. Emergency surgeries should not be delayed pending preoperative consultation. [I]

LOW-RISK

72. Clinically stable patients with COPD who are undergoing minor procedures under local anesthesia do not need preoperative testing. [I]
73. Clinically stable patients with mild to moderate COPD (FEV1 > 50 percent) who are undergoing any operation under general anesthesia do not need preoperative testing. [I]

HIGH-RISK

74. Patients with severe COPD (FEV1 < 50 percent) undergoing any operation that is done under general anesthesia should be considered for preoperative evaluation including pulmonary function test, gas exchange, and chest X-ray. [I]
75. Patients with severe COPD (FEV1 < 50 percent) planned for high-risk surgery should be referred to a pulmonary specialist. [I]

OPTIMIZATION OF PRE- AND POSTOPERATIVE CARE

76. Bronchodilator therapy should be optimized prior to planned surgery. [I]
77. Patients should be encouraged to quit smoking and instructed to stop smoking at least 6 to 8 weeks before surgery. [I]
78. Deep breathing, incentive spirometry, early mobilization, and adequate pain control should be encouraged to reduce postoperative pulmonary complications in patients with COPD. [I]
79. Patients who are on oral glucocorticoids should receive stress doses of intravenous glucocorticoids in the perioperative period to reduce the risk of adrenal insufficiency. [I]
80. Pulmonary consultation should be obtained prior to surgery in patients with an FEV1 below 35 percent predicted and in patients who are to undergo lung volume reduction surgery. [I]

Annotation N: Special Considerations for a Patient Planning to Travel at High Altitude

SPECIAL CONSIDERATIONS FOR A PATIENT PLANNING AIR TRAVEL

Patients with severe COPD who are on long-term oxygen therapy or have sea level PO₂ below 80 mm Hg should be evaluated pre-flight for supplementary oxygen during air travel. [C]

81. Perform pre-flight estimation of the expected degree of hypoxemia. [C] (See Table 7, Table 8)
82. Prescribe sufficient oxygen in flight to raise PO₂ (Alt) to around ~ 60 mm Hg. [C]
83. Warn patients with known bullous disease of the increased risk for pneumothorax during air travel. [C]
84. Arrange in-flight O₂ supplementation with the airline.

Table 7: How to Calculate Expected In-flight PO₂

Step 1:	Calculate expected in-flight PO ₂ (Alt) based on sea level PO ₂ (SL) and FEV1 according to the formula: $\text{PaO}_2 (\text{Alt}) = 0.453 [\text{PaO}_2\text{SL}] + 0.386 [\text{FEV1 \% predicted}] + 2.44$ Pre-calculated values of predicted in-flight PaO ₂ can be looked up in Table 8.
Step 2:	A flow rate of 1L/minute increases inspired PO ₂ by about 20 mgHg (2 liter/minute increases inspired PO ₂ by about 40 mm Hg)
Step 3:	Adjust the O ₂ flow for any comorbid conditions such as hypercapnia (aim for in-flight SaO ₂ ~90%), cardiac or cerebrovascular disease (aim for in-flight SaO ₂ > 95%)

The values of PaO₂(Alt), calculated from the above formula, for given values of PaO₂ (SL) in the range of 60 to 80 mm Hg and FEV1 from 30 to 100 percent predicted can be found in Table 8. If the PaO₂ (SL) is above 80 mm Hg, the patient probably does not need oxygen for travel.

Table 8: Predicted In-flight PaO₂ Based on PaO₂ at Sea Level and FEV1

FEV1 %Predicted		100	90	80	70	60	50	40	30
PaO ₂ at sea level	80	56.2	54.9	52.7	50.9	49.2	47.4	45.7	44.9
	70	51.6	49.9	48.1	46.4	44.6	42.9	41.1	39.4
	60	47.1	45.4	43.6	41.9	40.1	38.4	36.6	34.9

Dillard et al., 1989a



FOLLOW-UP/MONITORING

Annotation O: Continue Follow-up and Monitoring

SCHEDULE FOLLOW-UP

Patients with moderate to severe COPD should be reevaluated at least once a year. [I]

85. Patients with COPD should be assessed on a periodic basis, based on the severity and progression of their disease. [I]
86. Periodic evaluations of patients with COPD should include a review of their symptoms, their current treatment regimen, reported exacerbations, and spirometry testing. [I] (See Table 9)

Table 9: Evaluation of Patient with COPD

√	
Clinical Assessment	Prevention
	Smoking status & readiness to quit
	Vaccination
	Symptom control
	• breathlessness
	• exercise tolerance
	• exacerbation frequency
	• sleep disruption
	• cough & sputum
	Use of drug treatment
	• adherence
	• adverse effect
	• inhaler technique
	Manage complications (in severe COPD)
	• presence of cor pulmonale
	• presence of depression
• presence of sleep disorder	
• need for LTOT	
• change nutritional status	
Need for pulmonary rehabilitation	
Measurements	Spirometry FEV1 & FVC
	Calculate BMI
	MRC dyspnea score

PALLIATIVE CARE

Healthcare providers should assist patients with COPD and their families during stable periods of health to promote discussion about advanced care planning, including end-of-life care. [I]

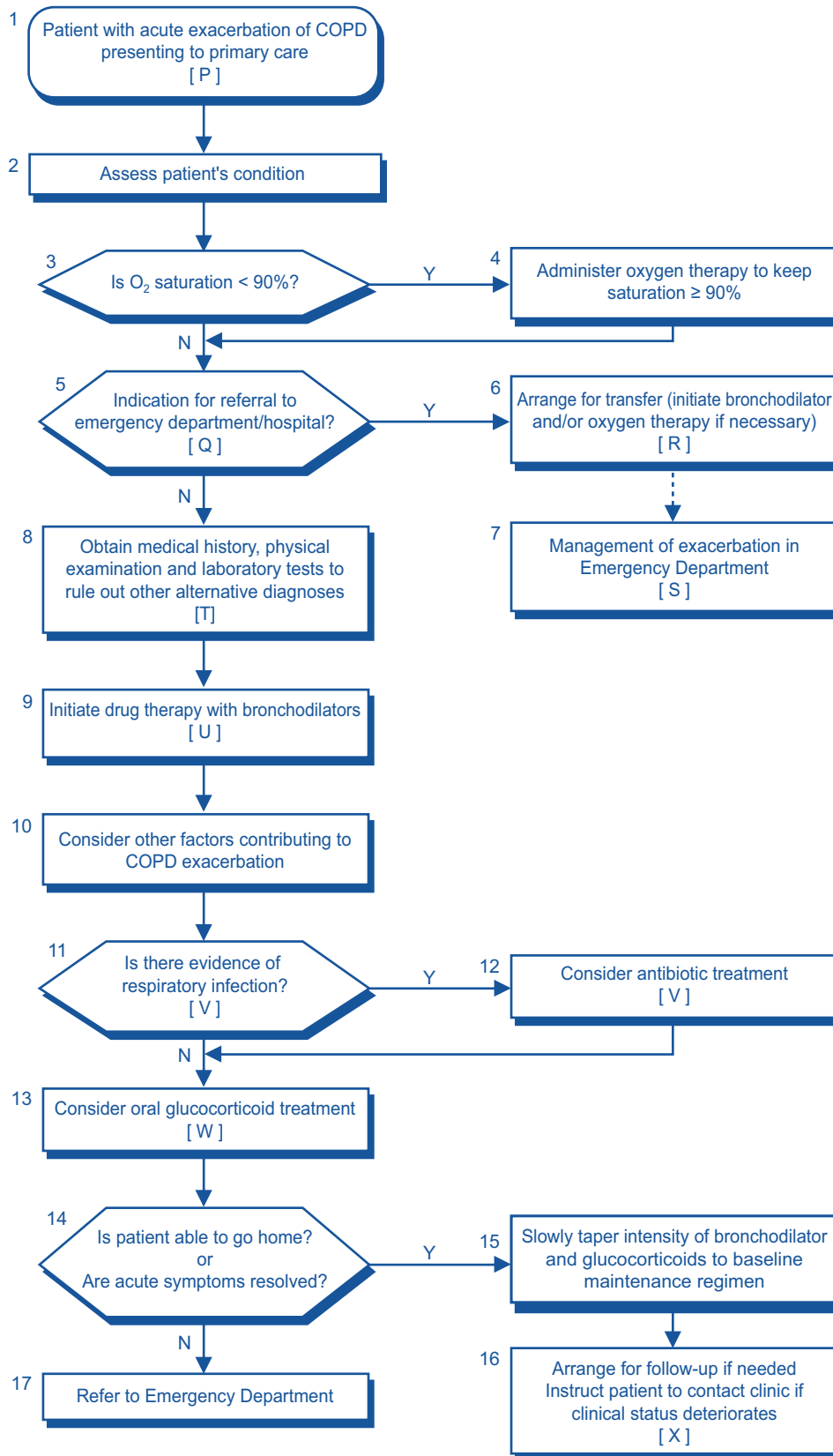
The clinical care team will provide regular, ongoing assessments of distressing symptoms (especially dyspnea) and actively seek to relieve suffering through a comprehensive approach to the physical, psychological, social, and spiritual aspects. [I]

87. Healthcare providers should assess the needs of patients with COPD and their families for advanced care planning and initiate advanced care in patients with poor prognosis (e.g., hospitalized with exacerbations). [I]
88. Patients with COPD and their families should be encouraged to participate in the planning and management of their treatment to improve their ability to cope with COPD in the future. [I]
89. The referral of the patient and their family to appropriate expertise in palliative care to assist in the relief of suffering may be considered when the patient/family's needs require such or are otherwise indicated. [I]



Module B: Acute Exacerbation

B



MODULE B: MANAGEMENT OF COPD ACUTE EXACERBATION ACTION STATEMENTS AND RECOMMENDATIONS

Annotation P: Patient with Acute Exacerbation of COPD Presenting to Primary Care

PATIENT WITH ACUTE EXACERBATION

An exacerbation is a sustained worsening of the patient's respiratory symptoms and function from his or her usual stable state that is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worse breathlessness, cough, increased sputum production, and change in sputum color. The change in the patient's condition often necessitates a change in medication.

REFERRAL TO THE EMERGENCY DEPARTMENT

Annotation Q: Are There Indications for Referral to the Emergency Department/Hospital?

CRITERIA FOR REFERRING TO THE EMERGENCY DEPARTMENT/HOSPITAL

More severe exacerbation or inadequate resources in the outpatient setting may require evaluation and management of the patient in the emergency department or a hospital setting. [I]

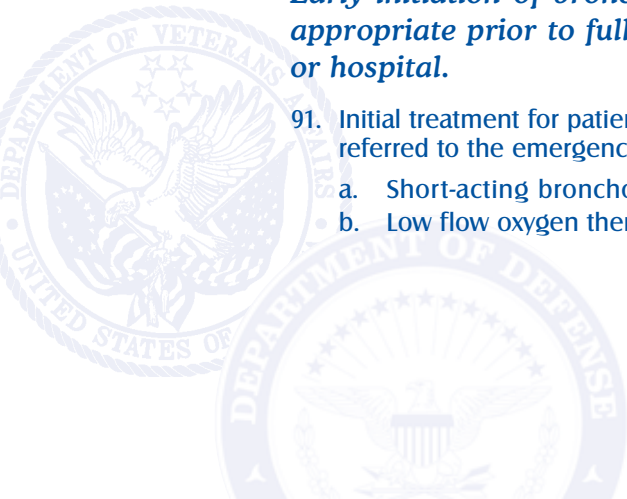
90. Patients evaluated for acute exacerbation of COPD should be considered for referral to the emergency department or admission to the hospital if they present with any of the following indications [I]:
- Unstable vital signs
 - Impaired level of consciousness or altered mental status
 - Severe breathlessness
 - New or worsening hypoxemia ($\text{SaO}_2 < 90$ percent)
 - Inadequate disease management resources at home
 - Lack of appropriate resources to evaluate or manage the patient in a clinic setting.

Annotation R: Arrange for Transfer to the Hospital

INITIATION OF SHORT-ACTING BRONCHODILATOR AND/OR OXYGEN THERAPY IF NECESSARY

Early initiation of bronchodilator therapy and oxygen (in hypoxemic patients) is appropriate prior to full assessment and treatment in the emergency department or hospital.

91. Initial treatment for patients experiencing an initial acute exacerbation of COPD who have been referred to the emergency department or admitted directly to the hospital should include [I]:
- Short-acting bronchodilator, by nebulizer or metered dose inhaler, if readily available
 - Low flow oxygen therapy to maintain SAO_2 at 90 percent.



Annotation S: Management of Exacerbation in the Emergency Department

ASSESSMENT OF ACUTE EXACERBATION IN THE EMERGENCY DEPARTMENT

In the emergency department, patients experiencing an acute exacerbation of COPD should be evaluated for the potential factors that contribute to the exacerbation. Assessment and treatment should proceed simultaneously in these patients. The emergency department should have the ability to perform these evaluations and treatments in a timely fashion. Increased respiratory symptoms in COPD can be due to a number of cardiac or pulmonary causes. Appropriate management mandates knowledge of the cause while simultaneously treating the severely ill patient.

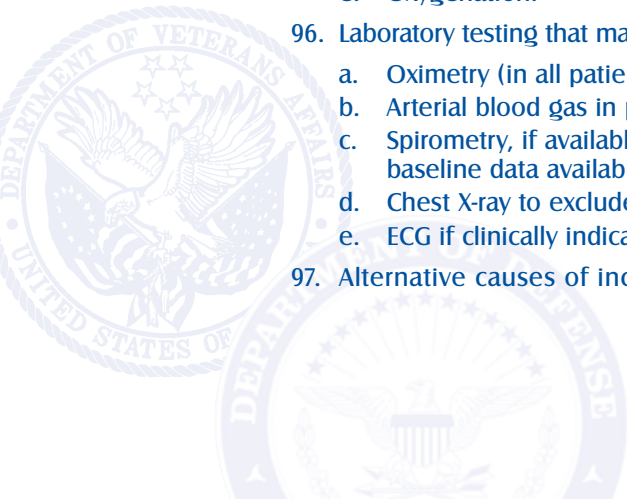
MANAGEMENT OF ACUTE EXACERBATION IN OUTPATIENT SETTING

Annotation T: Obtain Medical History, Physical Examination, and Laboratory Tests to Assess Severity, Rule Out Alternatives, and Confirm Diagnosis

ASSESSMENT, TESTING, AND DIAGNOSIS

Patients with COPD with acute exacerbation should be assessed to confirm the diagnosis, rule out other causes for worsening symptoms and determine the severity of the exacerbation, and the priorities for treatment.

92. The diagnosis of acute exacerbation of COPD should be confirmed and other causes excluded based upon clinical evaluation with additional diagnostic tests in selected cases. [I]
93. The severity of an exacerbation of COPD should be determined based upon medical history, symptoms, physical examination, and pulmonary function tests. [I]
94. Medical history with a patient with acute exacerbation should include:
 - a. Onset, duration, and type of symptoms (cough, sputum production, dyspnea, fever, decreased exercise tolerance, confusion, or acute mental status changes)
 - b. Current medication use
 - c. History of prior COPD exacerbations or hospitalizations (frequency, ICU admissions, and prior intubation)
 - d. The severity of the underlying COPD
 - e. Presence of comorbid conditions; e.g., heart disease.
95. Physical examination with a patient with acute exacerbation should include:
 - a. Vital signs
 - b. Level of consciousness
 - c. A careful pulmonary examination
 - d. Cardiovascular examination
 - e. Oxygenation.
96. Laboratory testing that may be considered with a patient with acute exacerbation:
 - a. Oximetry (in all patients with moderate or worse COPD)
 - b. Arterial blood gas in patients with deteriorating clinical status
 - c. Spirometry, if available, in patients who are able to perform the test and for whom there is baseline data available for comparison
 - d. Chest X-ray to exclude other causes if clinically suspected
 - e. ECG if clinically indicated.
97. Alternative causes of increased symptoms that need to be clinically excluded include:



- a. Congestive heart failure
- b. Pneumonia
- c. Pneumothorax
- d. Pulmonary embolism
- e. Cardiac ischemia
- f. Cardiac arrhythmia
- g. Upper airway infection; e.g., acute sinusitis
- h. Upper airway obstruction
- i. Pleural effusion
- j. Recurrent aspiration
- k. Noncompliance with medications
- l. Inappropriate oxygen therapy
- m. Adverse effects of medications; e.g., sedatives.

PHARMACOTHERAPY FOR ACUTE EXACERBATION IN OUTPATIENT SETTINGS

Annotation U: Initiate Drug Therapy with Bronchodilators

BRONCHODILATORS

Provide relief of symptoms and improve FEV1 with short-acting inhaled bronchodilator therapy. [B]

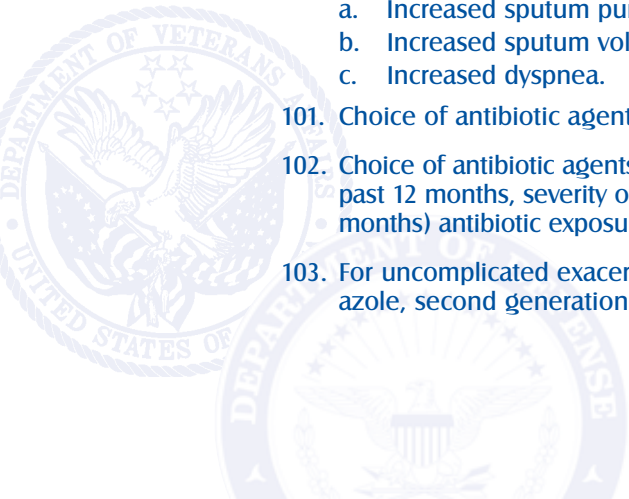
98. A short-acting bronchodilator (short-acting anticholinergic or short-acting beta 2-agonist) or a combination of both, using a metered dose inhaler with a spacer or aerosol mobilization, should be administered as soon as possible and as frequently as necessary. The choice of agent should be made on the basis of individual assessment and initial response to therapy. [B]
99. Methyxanthines should be avoided either orally or systemically since these agents may lead to side effects and have no proven efficacy in the setting of an acute exacerbation of COPD. [D]

Annotation V: Is There Evidence of Respiratory Infection?

ANTIBIOTICS

Prescribe a course of antibiotics for acute exacerbation of COPD if symptoms indicate bacterial infection; choice of antibiotic agent may be based on the degree of complication (number of exacerbations, FEV1, previous exposure to antibiotics, and cardiac disease).

100. COPD patients with acute exacerbation of COPD with at least two of the following will benefit from antibiotic therapy [A]:
 - a. Increased sputum purulence (change in sputum color)
 - b. Increased sputum volume
 - c. Increased dyspnea.
101. Choice of antibiotic agents may be determined based on local bacterial resistance patterns. [C]
102. Choice of antibiotic agents may be determined based on the frequency of exacerbations in the past 12 months, severity of underlying COPD, presence of cardiac disease, and recent (within 3 months) antibiotic exposure for each patient. [B]
103. For uncomplicated exacerbations of COPD, consider doxycycline, trimethoprim/sulfamethoxazole, second generation cephalosporin. [C]



104. For complicated exacerbations of COPD, consider beta-lactam/beta-lactamase inhibitor or fluoroquinolone. [C]

Stratifying the patient as complicated or uncomplicated may be helpful in determining the choice of antibiotic. (See Table 10)

Table 10: Determine Level of Patient Complication and Antibiotic Agents

Patient Characteristics	Antibiotic Agents
Uncomplicated Patients 1. Have experienced less than 3 exacerbations in the past 12 months 2. Have a baseline FEV1 of > 50% predicted 3. Do not have cardiac disease 4. Have not been exposed to antibiotics in the past 3 months	<ul style="list-style-type: none"> • Doxycycline • Trimethoprim/Sulfamethoxazole • Second or third generation cephalosporin • Extended spectrum macrolide
Complicated Patients 1. Have experienced 3 or more exacerbations in the past 12 months 2. Have a baseline FEV1 of < 50% predicted 3. Have cardiac disease 4. Have been exposed to antibiotics in the past 3 months	<ul style="list-style-type: none"> • Beta-lactam/beta-lactamase inhibitor • Fluoroquinolone^a

a By explicitly defining the patient that would benefit from the use of quinolone, the use of these drugs in uncomplicated exacerbations is discouraged.

Annotation W: Consider Oral Glucocorticoid Treatment

ORAL GLUCOCORTICOIDS

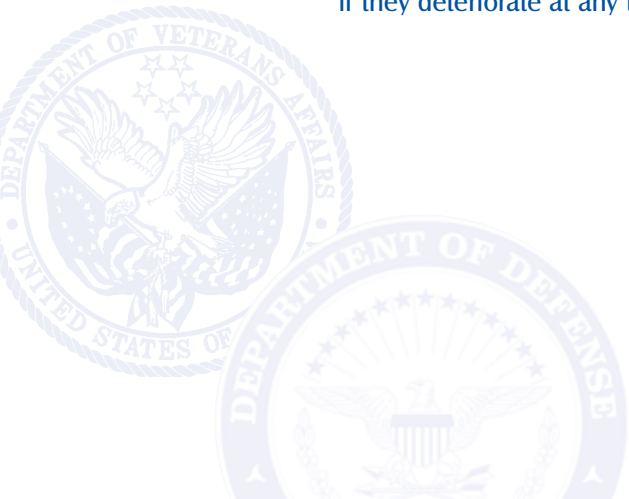
Consider a course of oral glucocorticoids in the treatment of an acute exacerbation of COPD to improve outcomes. [A]

105. A short course of oral glucocorticoids with a dose equivalent to 30 to 40 mg of prednisone per day (up to 14 days) should be considered for patients with COPD exacerbation. [A]

Annotation X: Arrange for Follow-Up if Needed

FOLLOW-UP

106. Patients should be instructed that if they have not improved with therapy over 48 to 72 hours or if they deteriorate at any time, they should seek attention from a healthcare provider. [I]



MODULE C: MANAGEMENT OF COPD PHARMACOTHERAPY ACTION STATEMENTS AND RECOMMENDATIONS

Bronchodilators: Short-Acting Bronchodilators in Patients with COPD (See Table C- 1, Table C- 2)

Consider using a maintenance short-acting anticholinergic and/or a maintenance short-acting beta 2-agonist in patients whose symptoms adequately respond to these drugs.

107. Short-acting beta 2-agonists should be used as rescue therapy as needed. [A]
108. Short-acting bronchodilators may be considered for maintenance for patients with COPD, as follows:
 - a. Short-acting anticholinergics (SAAC) or short-acting beta 2-agonists (SABA) to improve FEV1 and respiratory symptoms and reduce frequency of exacerbations [B]
 - b. Short-acting anticholinergics (SAAC) to improve QOL [B]
 - c. Insufficient evidence for short-acting beta 2-agonists (SABA) to improve QOL [I].
109. Since all chlorofluorocarbons (CFC) aerosols must be phased out, ipratropium CFC has been replaced by ipratropium hydrofluoroalkane (HFA). These two preparations may be considered in usual doses to improve FEV1 in patients with COPD. [B]

Bronchodilators: Long-Acting Inhaled Beta 2-Agonists in Patients with COPD (See Table C- 1, Table C-2)

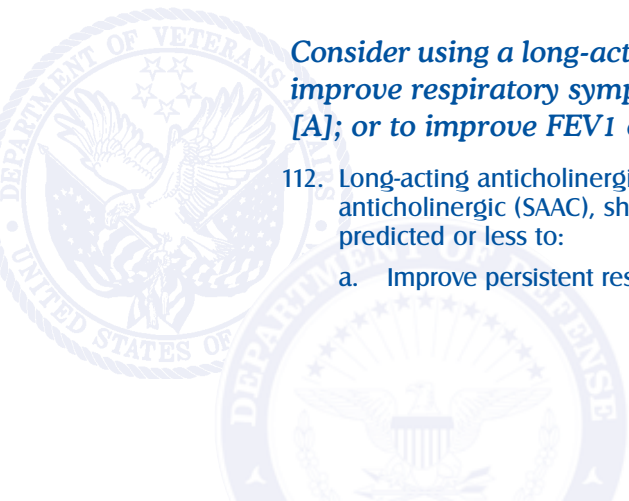
Consider using a long-acting inhaled beta 2-agonist (LABA) to improve QOL or respiratory symptoms such as dyspnea [A], and to reduce exacerbations [C].

110. Long-acting inhaled beta 2-agonists (LABA) should be considered for patients with COPD with an FEV1 70 percent predicted or less to:
 - a. Improve FEV1 [B]
 - b. Improve persistent respiratory symptoms such as dyspnea, or impaired health-related quality of life (QOL) [A]
 - c. Reduce exacerbations in patients who have had at least one exacerbation in the previous year and required glucocorticoids, antibiotics, or hospitalization [C].
111. In general, a long-acting inhaled beta 2-agonist (LABA) should not be substituted for a short-acting anticholinergic (SAAC) with the expectation of improving respiratory symptoms, quality of life (QOL), or exacerbations. [B]

Bronchodilators: Long-Acting Inhaled Anticholinergics in Patients with COPD (See Table C- 1, Table C- 2)

Consider using a long-acting inhaled anticholinergic (LAAC) in patients with COPD to improve respiratory symptoms and QOL or reduce moderate to severe exacerbations [A]; or to improve FEV1 or reduce hospitalizations [B].

112. Long-acting anticholinergics (LAAC), compared to placebo or maintenance short-acting anticholinergic (SAAC), should be considered for patients with COPD and an FEV1 65 percent predicted or less to:
 - a. Improve persistent respiratory symptoms such as dyspnea or impaired quality of life (QOL) [A]



- b. Reduce moderate to severe COPD exacerbations (i.e., exacerbations requiring antibiotics and/or oral or systemic glucocorticoids) [A]
 - c. Reduce COPD-related hospitalizations [B].
113. When a long-acting anticholinergic (LAAC) is used to improve patient outcomes in patients taking a short-acting anticholinergic (SAAC), the SAAC should be discontinued. [I] However, the use of a short-acting beta 2-agonist (SABA) as needed for rescue therapy should be continued.
114. In choosing long-acting bronchodilators, both long-acting anticholinergics (LAAC) and long-acting beta 2-agonists (LABA) provide similar benefits; however, there may be more modest improvement in FEV1 with LAAC. [B]

Combination Inhaled Bronchodilators

Combination bronchodilator therapy may be considered for patients with inadequate response to single agents to improve FEV1 and to reduce symptoms and/or exacerbations. [B]

115. When response to therapy with a short-acting beta agonist (SABA) is inadequate, consider the use of regularly scheduled combination SABA + short-acting anticholinergic (SAAC) to improve FEV1 and reduce exacerbations compared to treatment with the individual components. [B]
116. When response to regularly scheduled SAAC or combination of SABA + SAAC is inadequate, consider the use of combination SAAC + long-acting beta 2-agonist (LABA) to improve FEV1 and symptoms and reduce exacerbations compared to treatment with the individual components. [B]
117. When response to a LABA + SAAC or a long-acting anticholinergic (LAAC) alone is inadequate, consider the use of combination LABA + LAAC to improve FEV1. [B]
118. Consider the use of theophylline in addition to short-acting bronchodilators to improve FEV1. [B]
119. Consider the use of theophylline in addition to LABA to improve FEV1, symptoms, and quality of life (QOL) compared to therapy with the individual components. [B]
120. There is insufficient evidence to recommend that certain combinations are superior to other combinations, monotherapy with LAAC, or regimens including an inhaled glucocorticoid. Therefore, treatment selection should be based on patient-specific variables. [I]

Inhaled Glucocorticoids (See Table C- 3)

Consider adding inhaled glucocorticoids to optimize bronchodilator therapy in patients with COPD who have both severe disease (FEV1 < 50 percent predicted) and who have had at least one exacerbation in the prior year, to reduce the frequency of exacerbations. [A]

Alternatively, consider adding inhaled glucocorticoids in patients with severe COPD (FEV1 < 50 percent predicted) to improve FEV1, respiratory symptoms, and QOL. [B]

121. Inhaled glucocorticoids are not recommended in patients with mild to moderate COPD (FEV1 \geq 50 percent predicted) as there is little evidence of efficacy. [D]
122. Combination of a long-acting beta 2-agonist (LABA) and inhaled glucocorticoid may be considered in patients with severe COPD and at least one COPD exacerbation in the prior year to decrease the incidence of COPD exacerbations compared to therapy with the individual components. [A]
123. Combination of a long-acting beta 2-agonist (LABA) and inhaled glucocorticoid can be used in symptomatic patients with severe COPD to improve FEV1 (approximately 0 to 100 ml), symptoms and/or quality of life (QOL) [B]

124. There is insufficient evidence to recommend a specific choice or optimal dose when starting treatment with inhaled glucocorticoids. The doses used in efficacy trials or equivalent are suggested (fluticasone propionate 500 µg bid, budesonide 400 µg bid). [I]
125. Once treatment with inhaled glucocorticoids has been initiated, it is recommended to use caution when stopping the medication, as discontinuation may lead to COPD exacerbation. [B]
126. Patients should be informed about the potential side effects of inhaled glucocorticoids (oral candidiasis, bruising, adrenal suppression, cataracts, and osteoporosis). [B]
127. Treatment with inhaled glucocorticoids does not significantly affect the rate of decline in FEV1. [C]
128. Patients with COPD who are receiving oral or inhaled glucocorticoids should be evaluated for bone loss and considered for prevention or treatment of osteoporosis. [I]
129. The risks of long-term treatment with glucocorticoids should be discussed with the patient. [I]

Theophylline (See Table C- 4, Table C- 5)

Theophylline can be added to improve pulmonary function, symptoms, or activities in patients with COPD who do not achieve adequate symptom control with inhaled bronchodilators. [A]

130. Patients with COPD who do not achieve adequate symptom control with inhaled bronchodilators may be considered for adding theophylline therapy with an initial dose of 400 to 600 mg/day and a therapeutic target of blood level in the range 5 to 12 µg/ml). [A]
131. Blood levels should be carefully measured after initiation or change in dose. [I]
132. After the initial stability, repeat levels should be obtained when symptoms change, acute illness develops, potentially interacting drugs are added, noncompliance is suspected, dose adjustments are made, or symptoms suggestive of toxicity develop. [I]
133. If benefit has been demonstrated with a higher blood level (15 µg/ml of theophylline), careful monitoring is required. The risk-to-benefit ratio increases above a concentration of 12µg/ml, especially in older patients. [B]
134. Drug interactions with theophylline are common and may either increase or decrease theophylline metabolism. All changes in medical regimens should be evaluated for potential impact on theophylline levels. [C]
135. Theophylline should be continued only in patients who demonstrate a symptomatic benefit, such as improved dyspnea or exercise tolerance. The improvement in function from theophylline may not be evident in pulmonary function testing. However, therapy should be discontinued in patients who demonstrate no subjective or objective improvement after several weeks of theophylline therapy. [D]



Table C- 1. Inhaled Bronchodilators ^(a)

Drug	Dosage Form	Dosage	Maximum Dose	Nebulizer Dosage
Short-acting beta 2-agonists				
Albuterol 90 µg	MDI	1-2 puffs every 4-6 h ^b	12 puffs/day ^c	2.5 mg 3-4 times daily
Metaproterenol 0.65 mg	MDI	2-3 puffs every 3-4 h ^b	12 puffs/day ^c	10-15 mg 3-4 times daily
Pirbuterol 200 µg	MDI	1-2 puffs every 4-6 h	12 puffs/day	Not available
Levalbuterol 45 µg	MDI	1-2 puffs every 4-6 h	12 puffs/day	0.63–1.25 mg 3 times daily
Long-acting beta 2-agonists				
Formoterol 12 µg	DPI (capsules)	12 µg every 12 h	12 µg every 12 h	Not available
Salmeterol 50 µg ^d	DPI	50 µg every 12 h	50 µg every 12 h	Not available
Short-acting anticholinergics				
Ipratropium 18 µg	MDI	2 puffs every 6 h ^b	12 puffs/day ^c	0.25–0.5 mg every 6-8 h
Long-acting anticholinergics				
Ipratropium 18 µg	DPI (capsules)	18 µg once daily	18 µg once daily	Not available
Combination bronchodilators				
Albuterol 90 µg + ipratropium 18 µg	MDI	2 puffs every 6 h	12 puffs/day	2.5 mg/0.5 mg administered 4 times daily

MDI – Metered dose inhaler; DPI – Dry Powder Inhaler

- a Dosing information obtained from AHFS Drug Information 2005 and product package inserts
- b These are usual recommended **maintenance** doses, although they may be modified in particular clinical circumstances
- c Maximum doses per manufacturer's recommendations, although higher doses have been used clinically
- d Also available in the following combination products: fluticasone 100 µg/salmeterol 50 µg; fluticasone 250 µg/salmeterol 50 µg; fluticasone 500 µg/salmeterol 50 µg

Table C- 2. Oral Beta-Adrenergic Agonists

Drug	Oral Dose	Precautions
<u>Albuterol</u>		
Immediate release	2-4 mg tid qid	<ul style="list-style-type: none"> • Instruct patient to report palpitations, tachycardia, chest pain, muscle tremors, dizziness, headache, flushing, difficult urination, or breathing difficulty • Oral agents should be reserved for patients unable to use inhaled dosage forms as the risk of adverse effects significantly increase with the oral beta 2-agonists
Sustained release	4-8 mg every 12 h	
Metaproterenol	20 mg bid tid	
Terbutaline	2.5-5 mg tid qid	

Dosing information obtained from AHFS Drug Information 2005



Table C- 3. Inhaled Glucocorticoids^{a,b}

Inhaled Glucocorticoid	Dosage forms	Usual dosing interval	Low dose µg/day	Medium dose µg/day	High dose µg/day	Maximum dose per MFR (µg/day)
Beclomethasone 40 µg 80 µg	MDI	every 6-8h or every 12h	100-250 (2-6 puffs) (1-3 puffs)	250-500 (6-10 puffs) (3-5 puffs)	> 500 (> 10 puffs) (> 5 puffs)	640
Budesonide 200 µg ^c	MDI	every 12h	200-600 (1-3 inhalations)	600-1000 (3-5 inhalations)	> 1000 (> 5 inhalations)	1600
Flunisolide 250 µg	MDI	every 12h	500-1000 (2-4 puffs)	1000-2000 (4-8 puffs)	> 2000 (> 8 puffs)	2000
Fluticasone ^d 44 µg 110 µg 220 µg	MDI	every 12h	88-264 (2-6 puffs) – –	264-660 (6-15 puffs) (2-6 puffs) (1-3 puffs)	> 660 (> 15 puffs) (> 6 puffs) (> 3 puffs)	1760
Mometasone 220 µg	DPI	every 24h or every 12h	200-400	400-800	> 800	880
Triamcinolone 100 µg	MDI	every 6-8h or every 12h	400-1000 (4-10 puffs)	1000-2000 (10-20 puffs)	> 2000 (> 20 puffs)	1600

MDI – Metered dose inhaler; DPI – Dry Powder Inhaler

- a Not approved by the FDA for COPD. Beclomethasone, budesonide, fluticasone, and triamcinolone have been studied in clinical trials in COPD. The combination of fluticasone and salmeterol is approved by the FDA for COPD.
- b Dosing adapted from Global Initiative for Asthma 2005 and Global Strategy for Asthma Management and Prevention 2004 update
- c Also available in a formulation for use with a jet nebulizer (currently indicated for pediatric asthma)
- d Also available in the following combination products: fluticasone 100 µg/salmeterol 50 µg; fluticasone 250 µg/salmeterol 50 µg; fluticasone 500 µg/salmeterol 50 µg



Table C- 4. Theophylline

	Starting dose		Maintenance dose
Adults (16-60 years) Without Risk Factors for Impaired Clearance	Initial dose 400 mg/day	If using prompt release tablets, divide daily dose every 6-8 hours	If serum concentration < 5 µg/ml and symptoms are not controlled, increase daily dose by 25%
Patients with risk factors for impaired clearance, (e.g., age > 60 years, patients with liver disease or congestive heart failure, or those in whom it is not feasible to monitor serum theophylline concentrations)	Initial dose should not exceed 300 mg/day	Dosing may also be initiated with the 12-hour extended release products In general, once daily products (e.g., Uniphyll or Theo-24) should not be used when initiating theophylline	If serum concentration 5–12 µg/ml and symptoms are controlled and dosage tolerated, maintain dose. If symptoms are not controlled, increase dose by 25%. In general, serum concentrations should not exceed 15 µg/ml

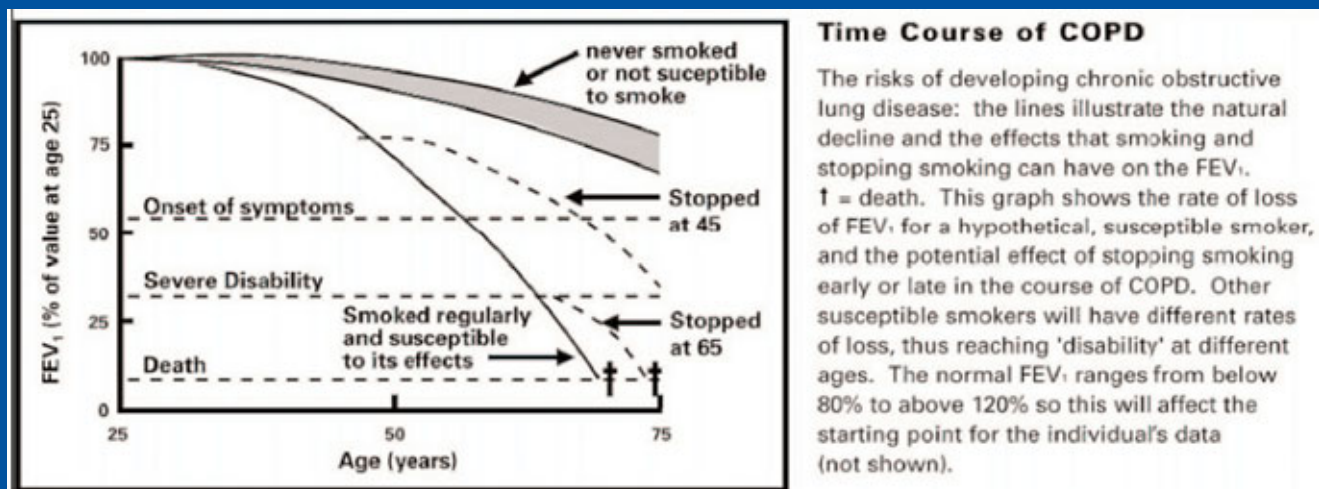
Dosage increases should be made only if the previous dose has been tolerated and at intervals no less than 3 days.
For extended release products, serum concentration should be measured approximately 8 hours post-dose.

Table C- 5. Factors That Can Affect Theophylline Levels ^a

Drugs or factors decreasing theophylline clearance	Drugs or factors increasing theophylline clearance
cimetidine, ciprofloxacin, clarithromycin, disulfiram, enoxacin, erythromycin, mexiletine, pentoxifylline, propranolol, ticlopidine, troleandomycin, zileuton, allopurinol (≥ 600 mg/day), fluvoxamine, interferon, propafenone, tacrine, verapamil Congestive heart failure, cor pulmonale, elderly (> 60 years), hepatic insufficiency ^b (cirrhosis, acute hepatitis, cholestasis), fever (> 24 hours)	Charcoal broiled food; low carbohydrate, high protein diet Smoking (tobacco or marijuana); henobarbital; phenytoin; rifampin, carbamazepine; isoniazid; moricizine

^a List is not intended to be inclusive of all potential drug interactions

^b Theophylline clearance has been decreased by 50 percent or more

Figure 1. Time Course of COPD

Reference: Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J.* 1977 Jun 25;1(6077):1645–8.

Table C- 6. Caution and Special Instruction for Medication

Drug Class	Cautions
Beta 2-agonists	<ul style="list-style-type: none"> • May cause palpitations, chest pain, rapid heart rate, increased blood pressure, tremor, nervousness • Decreases in potassium levels have occurred • Short-acting beta 2-agonists are used for acute treatment of bronchospasm • Long-acting beta 2-agonists are not to be used for acute treatment of bronchospasm • Formoterol: capsules are for oral inhalation only; not to be taken by mouth; administer using supplied inhalation device (Aerolizer) only
Anticholinergics	<ul style="list-style-type: none"> • Use with caution in patients with narrow angle glaucoma, prostatic hyperplasia, or bladder neck obstruction • Caution patient to getting product in eyes; temporary blurred vision may result • For relief of dry mouth, suggest use of saliva substitute, practice of good oral hygiene, rinsing of mouth after inhalation; instruct patient to take sips of water frequently, suck on ice chips or sugarless hard candy, or chew sugarless gum • Not indicated for initial treatment of acute episodes of bronchospasm • Tiotropium: capsules are for oral inhalation only; not to be taken by mouth; administer using supplied inhalation device (HandiHaler) only
Inhaled glucocorticoids	<ul style="list-style-type: none"> • Localized fungal infections with <i>Candida albicans</i> or <i>Aspergillus niger</i> have occurred in the mouth, pharynx, and occasionally the larynx • Advise patients to rinse mouth after inhalation • Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported • Risk of skin thinning and bruising may be increased • Decreased bone density may occur with long-term use in patients with COPD • Increased risk of developing pneumonia
Theophylline	<ul style="list-style-type: none"> • Carefully monitor patients with history of arrhythmias, seizures, peptic ulcer, or gastroesophageal reflux • Monitor theophylline levels; the usual therapeutic range is 7 to 20 µg/mL but some toxicity may be noted at the upper end of this range • Common adverse reactions include stomach upset, nausea, insomnia, tremors, palpitations, exfoliative dermatitis, and urticaria • Instruct patient not to take extra doses of theophylline for acute asthma attack • Sustained-release products should not be crushed or chewed • Scored tablets may be split without affecting absorption characteristics



ACRONYM LIST

AAT	Alpha 1-Antitrypsin
ATS	American Thoracic Society
BMI	Body Mass Index
CFC	Chlorofluorocarbons
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
DPI	Dry Powder Inhaler
ERS	European Respiratory Society
FEV1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
HFA	Hydrofluoroalkane
LAAC	Long-Acting Anticholinergic
LABA	Long-Acting Inhaled Beta 2-agonist
LTOT	Long-Term Oxygen Therapy
LVRS	Long Volume Reduction Surgery
MDI	Metered Dose Inhalers
MMRC	Modified Medical Research Council
MRC	Medical Research Council
NAC	N-Acetylcysteine
QOL	Quality of Life
SAAC	Short-Acting Anticholinergic
SABA	Short-Acting Beta 2-agonist
VC	Vital Capacity

