Medical Advisory Panel for the
Pharmacy Benefits Management
Strategic Healthcare Group

The Pharmacologic Management of Chronic Obstructive Pulmonary Disease

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THE PHARMACOLOGIC MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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The Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group

Mission

The role of the Medical Advisory Panel (MAP) in the PBM SHG is to consult on development and refinement of evidence-based pharmacologic management guidelines for the VHA. These guidelines are intended to promote provision of quality, cost effective patient care.

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Pharmacy Benefits Management (PBM)
Strategic Healthcare Group (SHG)

VHA's PBM SHG has been directed by the Under Secretary for Health to coordinate the development of guidelines for the pharmacologic management of common diseases treated within the VA, establish a national level VA formulary, and to manage pharmaceutical costs, utilization, and measure outcomes as they apply to patient care. The MAP provides support and direction to the PBM SHG staff, located in Washington DC and Hines, Illinois.

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Guideline Development Process

Summary

This consensus and evidence-based guideline on the pharmacologic management of patients with chronic obstructive pulmonary disease is intended to update the 1999 publication. Whenever possible, the PBM and MAP relies upon evidence-based, multidisciplinary, nationally recognized consensus statements for the basis of VA guidelines. Relevant literature is reviewed and assessed with consideration given to the VA population. Draft guidelines are sent to the field for comments prior to being finalized.

Development Process and Sources of Information

Development of the guidelines relied upon the following consensus documents:

Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. NHLBI/WHO workshop report. www.goldcopd.com

Bach PB, Brown C, Gelfand SE, American College of Physicians-American Society of Internal Medicine; American College of Chest Physicians**.** Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 2001; 134:600-20.

American Thoracic Society Statement. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Resp Crit Care Med 1995; 152:S78-S121.

British Thoracic Society Guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997; 52(suppl 5): S1-S28.

Siafakas NM et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD): A consensus statement of the European Respiratory Society (ERS). Eur Respir J 1995; 8:1395-1420.

Department of Veterans Affairs Clinical Practice Guidelines for the Management of Persons with Chronic Obstructive Pulmonary Disease or Asthma. Publication No. 99-0012.

The algorithm and annotations are in part based on the COPD guideline developed in 1999. To update this information, the literature following the publication of the 1999 document was searched (search queried articles published from March 1999 to December 2001). A literature search of MEDLINE was conducted combining the search terms chronic obstructive pulmonary disease and COPD with the following: beta adrenergic agonists, albuterol, salbutamol, metaproterenol, pirbuterol, bitolterol, salmeterol, formoterol, ipratropium, theophylline, inhaled corticosteroids, inhaled steroids, corticosteroids, steroids, fluticasone, budesonide, beclomethasone, flunisolide, triamcinolone, prednisone, methylprednisolone, acute exacerbation, antibiotics. The literature was limited to clinical trials, adult human subjects and articles published in the English language. Using this strategy, 102 clinical trials were found. Nineteen were used in the development of this guideline. The others were excluded for the following reasons: drug or formulation not available in the United States (n=15), ventilator-related articles (n=11), outside the scope of the document (n=30), small studies or studies of short duration where larger and/or longer duration studies available (n=15), studies involving inflammatory or cellular mediators, etc. (n=7), asthma study (n=1), other (n=4). The bibliographies of articles and consensus documents were reviewed for additional relevant literature. Literature known to the PBM-MAP on medical history, physical examination, diagnosis and evaluation was also included in the document.

Consensus articles, meta-analysis, and systematic reviews were included as references for the following topics: smoking cessation, pulmonary rehabilitation, nutritional support, immunizations, and management/prevention of steroid induced osteoporosis.

Methods to Formulate Recommendations

The referenced articles have been assigned a grade of evidence and strength of recommendation rating, which is based on AHCPR guideline development (Agency for Health Care Policy and Research publication (No. 93-0550, March 1993). A description of this tool is provided below:

Level of Evidence

- **A-** Large, randomized trials with clear-cut results (low risk of error)
- **B-** Small, randomized trials with uncertain results (moderate to high risk of error)
- **C-** Nonrandomized, historical and expert opinions; uncontrolled studies, case series.

Strength of recommendation

I - Usually indicated, always acceptable and considered useful and effective.
IIa – Acceptable, of uncertain efficacy and may be controversial. May be helpful, not likely to be harmful.
IIb – Acceptable, of uncertain efficacy and may be controversial. Not well established by evidence, can be helpful and probably not harmful.
III – Not acceptable, of uncertain efficacy and may be harmful. Does not appear in the guidelines.

Algorithms

The symbols used in the algorithm are described below:

Oval – Represents the start of the algorithm that defines the patient population.
Rectangle – Represents a process, such as a diagnostic or therapeutic intervention.
Hexagon – Represents the point where a decision needs to be made.
Circle – Represents the point where the algorithm terminates or refers to another algorithm.

Information supporting the algorithms can be found in the accompanying text.

Use of the Guidelines

The guidelines are meant to focus on the pharmacologic management of patients with COPD. Other sections have been included that highlight areas such as physical examination, diagnosis, nonpharmacologic management, etc. Practitioners should refer to pulmonary texts or local experts for the finer points of diagnosis and these other areas.

The purpose of the guidelines is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. This guideline attempts to define principles of practice that should produce high quality patient care. They are attuned to the needs of a primary care practice but are directed to providers at all levels. Regardless of the setting in which patients with COPD are cared for, the clinician is encouraged to follow these and other COPD guidelines and to use clinical judgment of when to refer to a specialist. This will depend on the skill and experience of managing patients with COPD, and also the resources available to the practitioner.

Updating the Guidelines

PBM will review the guidelines routinely. Updating will occur as new information is made available from well-designed, scientifically valid studies and as outcome data may direct. Any member of the VA community is encouraged to recommend changes based on such evidence.

A current copy of the pharmacologic management guidelines can be obtained from the PBM home page at http://www.vapbm.org or http://vaww.pbm.med.va.gov.

Acknowledgments*

The MAP collaborates with VA technical advisory groups and other experts in developing guidelines. We gratefully acknowledge and thank those clinicians for sharing their expertise in this area.

Draft guidelines were disseminated for peer-review through the VISNs, prior to their completion. The MAP and the PBM would like to acknowledge and thank all individuals who contributed both their time and effort to this process.

The following Participant List does not represent all the clinicians who reviewed the guideline, rather those who wished to be acknowledged. The Medical Advisory Panel and Pharmacy Benefits Management take full responsibility for the content of this guideline.

This list may not include clinicians who reviewed previous publications of this guideline (refer to Publ. # 96-0001)

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EXECUTIVE SUMMARY

1. Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in North America. The mortality rate continues to rise. Tobacco smoking accounts for 80 - 90% of the risk for developing COPD. Cessation of tobacco smoking helps reduce the rate of decline in FEV_1.

2. Therapy should include patient education, vaccinations, regular exercise, dietary support, and close follow-up of response to pharmacological treatment. Oxygen therapy can reduce the risk of cor pulmonale and death in hypoxemic patients.

3. Pharmacotherapy for chronic management
   a. Ipratropium is an effective bronchodilator for the treatment of COPD; it may cause less toxicity than β_2-adrenergic agonists during long-term therapy.

   b. The short-acting β_2-adrenergic agonist metered-dose inhalers (MDIs) such as albuterol, are generally effective agents for either as-needed (prn) or regular administration.

   c. Salmeterol and formoterol are long-acting β_2-adrenergic agonists. They may have a potential role for patients with significant nocturnal dyspnea, for those requiring more than 12 inhalations per day of short-acting β_2-adrenergic agonists, or patients requiring maintenance ipratropium, but are unable to comply with four times a day dosing or doses requiring a large number of puffs per day.

   d. Theophylline may be added if response to inhaled bronchodilators is inadequate. This drug requires close monitoring and should be continued only for patients who demonstrate a beneficial response.

   e. Long-term use of high-dose inhaled steroids in patients with moderate-severe COPD may reduce the frequency or severity of exacerbations, and unscheduled clinic care. A six-week trial of high dose inhaled steroids is adequate to evaluate symptomatic response; however, to see improvement in exacerbation rates or severity, a longer trial may be necessary (eg. 6 months). Patients not responding to inhaled steroids may be candidates for a short-term oral steroid trial. If no benefit is demonstrated with either oral or inhaled steroids, they should be discontinued.

4. Management of acute exacerbations
   a. Short-acting β_2-adrenergic agonists are the bronchodilators of choice to treat COPD exacerbations and may be administered via a MDI with spacer. If the patient is unable to benefit from the MDI with spacer, administration via nebulizer can be used.

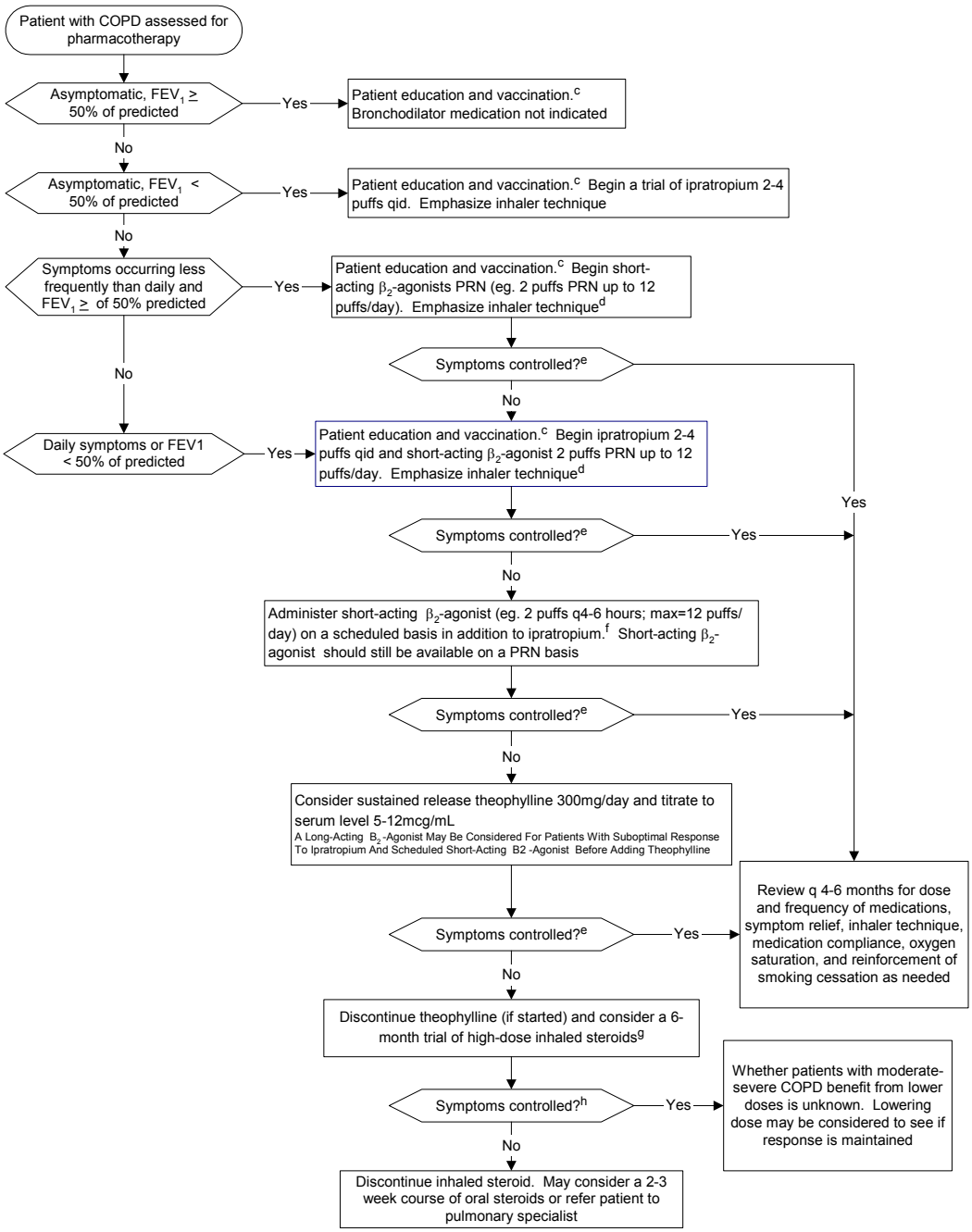
   b. The effect of ipratropium is similar to β_2-adrenergic agonists. Because ipratropium has a slower onset of action, β_2-adrenergic agonists are generally preferred during acute exacerbations. There are insufficient data as to whether combining ipratropium with β_2-adrenergic agonists provides additional benefit.

   c. Systemic steroid (IV/oral) administration can improve pulmonary function and decrease relapse rates in patients requiring hospitalization. It is unclear if exacerbations that do not require hospitalization merit systemic steroid administration. However, systemic corticosteroids should be considered for patients on maintenance oral or inhaled steroids; patients who have recently stopped oral steroids; patients who have had a prior response to oral steroids; patients with a low oxygen saturation (< 90%); patients with PEFR < 100L/min; or patients not responding to initial bronchodilator therapy.

   d. Treatment with antibiotics may be reasonable for exacerbations associated with changes in sputum (quality, volume, or color), and increased dyspnea, cough or fever. Presence of an infiltrate on chest radiograph suggests pneumonia; the patient should be treated with antibiotics as deemed appropriate.

   e. Due to minimal evidence of efficacy and potential risk of toxicity, the role of theophylline in acute COPD exacerbation is questionable.

Algorithm 1
Outpatient Pharmacotherapy of COPD[a, b]



[a] This algorithm shows a step-by-step progression of therapy with advancement of COPD severity. Patients enter the algorithm at different levels depending on severity of disease and current drug therapy.

[b] Pulmonary referral may be requested at anytime at the provider's discretion. The decision to treat patients with COPD should be based on the familiarity and experience of the provider.

[c] Patient education: smoking cessation and protection from enviromental pollutants and allergens. Vaccination: pneumococcal and annual influenza.

[d] If patient cannot use MDI, dry powder inhaler may be tried. Nebulizers may be justified in patients with advanced disease who cannot use other inhalers effectively.

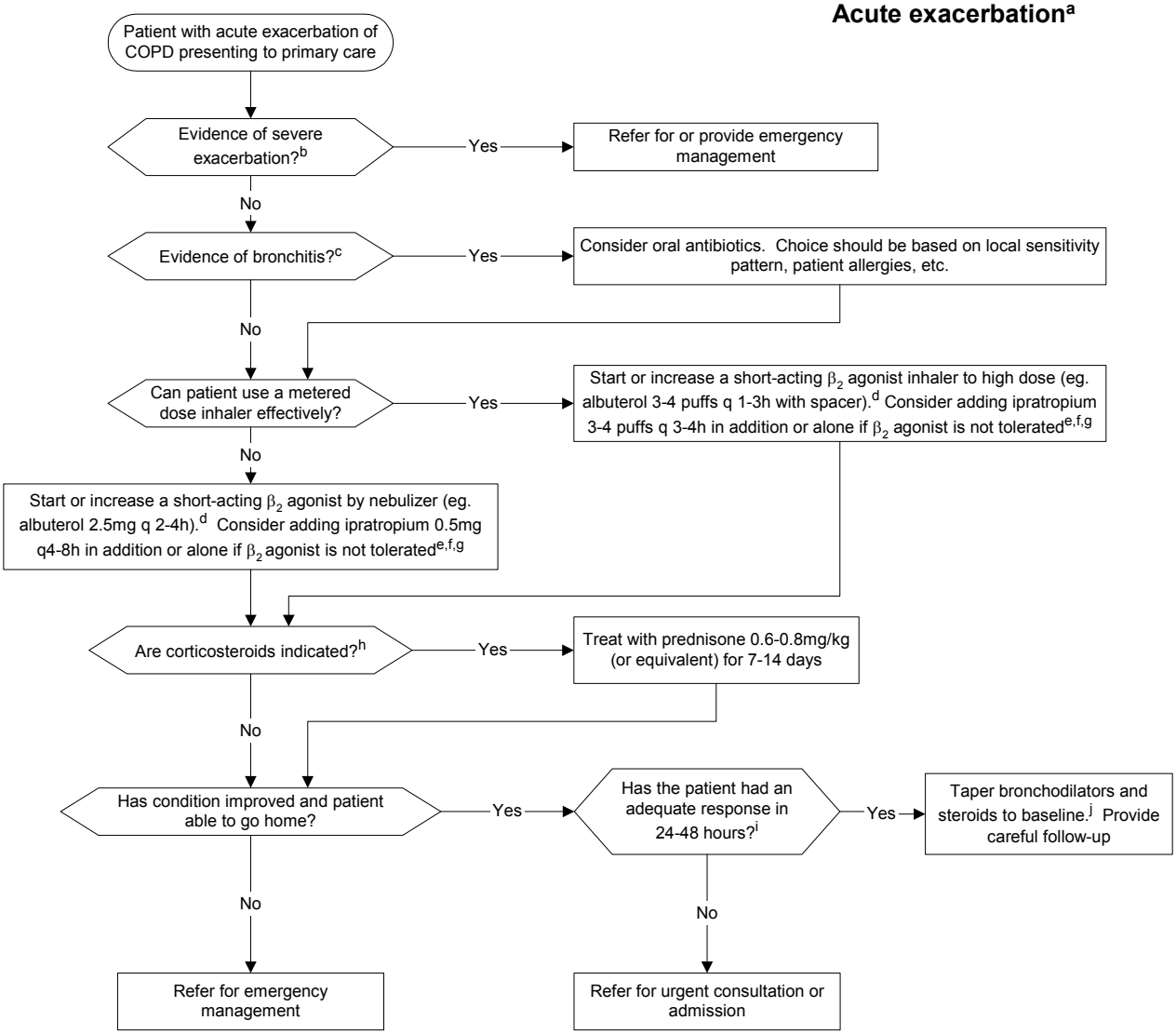
[e] Assess patient adherence to therapy, review inhaler technique, titrate dosage of existing therapy before moving to the next step of the algorithm.

[f] Long-acting β_2-agonists may be considered for those unable to comply with frequent administration of short-acting β_2-agonists or ipratropium, or in patients with nocturnal dyspnea.

[g] In some cases, doses exceeding the manufacturers recommended dose may be necessary, as were used in some clinical trials.

[h] As determined by symptomatic benefit, decreased frequency or severity of exacerbations, or improvement in FEV1 > 20% predicted.

Algorithm 2
Acute exacerbation[a]



[a]Adapted from the ATS guidelines, BTS guidelines, VHA guidelines for COPD/asthma, GOLD report, ACP-ACCP report

[b]Mental status changes, dyspnea at rest, respiratory rate > 25/min, heart rate > 110/min, cyanosis, use of accessory muscles, or pO2 <60mmHg.

[c]Increase in volume of sputum, presence of purulent sputum, increased cough, dyspnea, fever; presence of an infiltrate on chest X-ray suggests pneumonia and should be treated with antibiotics as deemed appropriate.

[d]For severe exacerbations, maximum dosages of short-acting β_2 agonists are 6-8 puffs q1/2-2h by MDI or 2.5mg q 1/2-2h by nebulizer.

[e]Maximum dosage of ipratropium is 6-8 puffs q 3-4h with a spacer.

[f]There is no evidence that addition of ipratropium provides added clinical benefit.

[g]If the patient is not responding to the above measures, adding theophylline can be considered although there are little data on its effectiveness in this setting. If the patient is already taking theophylline, the dose should be adjusted to achieve a level of 5-12mcg/ml.

[h]Possible indications for steroids include: patient already on steroids, prior response to steroids, recently stopped steroids, not responding to initial bronchodilators, patient's first presentation.

[i]Decrease in cough, dyspnea, sputum production, respiratory rate, heart rate, increase in function and endurance.

[j]No study has evaluated the need to taper; however many clinicians include a taper as part of the treatment course.

I. DEFINITION

Chronic obstructive pulmonary disease (COPD) is characterized by the presence of airflow obstruction, principally due to chronic bronchitis or emphysema. The airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.

II. GENERAL PRINCIPLES

A. EPIDEMIOLOGY

COPD is the fourth leading cause of death in North America and its mortality rate is rising. It is estimated to affect 15 million Americans and the prevalence is increasing. It affects 4-6% of adult males and 1-3% of adult females in the U.S.

In 1996 within the VA, more than 126,267 patients were discharged with a primary or secondary diagnosis of obstructive lung disease. This accounted for approximately 33% of all patients admitted to medical services and approximately 16% of all VA hospital admissions. In the outpatient setting, approximately 1 million visits had obstructive lung disease listed as a primary or secondary diagnosis.

B. RISK AND PROGNOSTIC FACTORS

1. Tobacco smoking accounts for 80 to 90% of the risk of developing COPD.
2. Smoking is a greater risk factor for developing COPD than are occupational exposures.
3. α_1-antitrypsin deficiency is a rare, but important cause of early onset COPD.
4. Age, FEV_1, severity of hypoxemia, presence of hypercapnia, and cor pulmonale are prognostic factors.

III. PATIENT EVALUATION

The diagnosis of COPD should be considered in patients with a current or prior history of chronic cough present intermittently or daily, current or prior history of chronic sputum production, dyspnea, and history of significant exposure to risk factors (tobacco, occupational/environmental exposure).

Alpha1-antitrypsin (AAT) deficiency accounts for less than one percent of COPD. ATT deficiency may be suspected in patients with moderate-severe COPD before the age of 50, a family history of ATT, chronic bronchitis with airflow obstruction in a person who has never smoked, bronchiectasis, in the absence of clear risk factors, or cirrhosis without apparent risk factors. Referral to specialist should be considered.

A. HISTORY

1. Smoking history: Age at initiation, pack-year history, smoking cessation history, current smoking status, and willingness to quit.

2. Extent, severity, frequency and duration of symptoms: cough, dyspnea, sputum volume and character, wheezing, and activity limitation.

3. Environmental and occupational exposure history.

B. PHYSICAL EXAMINATION

The sensitivity of physical examination is low for diagnosing mild or moderate COPD. Physical signs of COPD include wheezing, prolonged forced expiratory time, decreased breath sounds, decreased ribcage expansion and diaphragmatic excursion, thoracic hyperresonance, subxyphoid cardiac apical impulse, and use of accessory muscles. However, the presence or absence of these signs does not clearly reflect the degree of airflow limitations.

C. SPIROMETRY

Measurement of FEV_1 is important to establish airway obstruction, define severity, indicate prognosis, and measure response to therapy and progression of disease. Spirometry (**pre- and post-bronchodilation**) is required to confirm presence and reversibility of airflow obstruction and to quantify the maximum level of ventilatory function. Peak expiratory flow rate (PEFR) is not as accurate as FEV_1 in assessing lung function or airway obstruction in COPD and may underestimate the degree of airflow obstruction.

D. OTHER TESTS

1. Electrocardiogram: ECG helps indicate the presence of late cor pulmonale.

2. Arterial Blood Gas: A resting arterial blood gas after 30 minutes on room air remains the standard for determining the need for oxygen therapy. It also is important for the diagnosis of respiratory failure.

3. Chest X-ray: CXR can detect lung hyperinflation, bullae, pulmonary hypertension, cor pulmonale, and pneumothorax. It is suggestive of emphysema when the disease is severe and may be helpful when the disease is moderate. It is also used to help exclude other pulmonary diseases.

IV. MANAGEMENT OF COPD

A. GENERAL APPROACH

1. Management of stable COPD aims to: avoid or minimize adverse effects of treatment, reduce symptoms, prevent and treat complications, prevent and treat exacerbations, reduce the decline in lung function, improve quality of life, and increase survival.

2. It is important to educate the patient and family about the disease and treatment; encourage an active, healthy lifestyle; obtain agreement of goals in treatment and provide supportive follow-up. Cooperative self-management should be fostered.

3. Principles of management include: smoking cessation, bronchodilation, suppression of inflammation, treatment of infection, mobilization of secretions, and support with oxygen to maintain adequate oxygenation.

4. For the primary care provider, a pulmonary specialist consult should be considered for unstable disease not controlled by therapy, frequent hospital admissions, difficult treatment decisions, such as instituting oral or high dose inhaled corticosteroids, etc. The threshold for consultation should depend on the level of expertise of the provider. Once stable, the patient should be referred back to the primary care physician for long-term management.

B. NON-PHARMACOLOGIC THERAPY

1. Smoking cessation

Smoking cessation can reduce the rate of decline in FEV_1 to near that in non-smokers. As the only disease modifying intervention available, it should be emphasized at each clinic visit.[6-10] **LE=A, SR=I**

Patients should be encouraged to participate in an intensive smoking cessation program. Nicotine replacement in conjunction with a comprehensive therapy program can be an effective strategy, with a smoking cessation success rate of 20-40% at 6 months in some studies. Other agents with evidence of benefit in smoking cessation include bupropion and nortriptyline. A full review of agents used in smoking cessation is beyond the scope of this guideline. For a full review, refer to the VHA/DoD Guideline on Smoking Cessation and the U.S. Public Service Report Treating Tobacco Use and Dependence: A Clinical Practice.[11, 12]

2. Regular exercise

An informal program, with an emphasis on walking and upper body exercise, may help maintain physical functioning. In more advanced disease, formal exercise training can be part of a comprehensive rehabilitation program that may be beneficial.[13-15]

3. Nutritional support

Under nutrition is associated with respiratory muscle weakness and increased mortality. The most-cost effective method for nutritional support in undernourished patients has not been established. It is important in non-obese COPD patients to prevent weight loss.[16] For any patient with poor appetite or eating-related dyspnea, frequent small meals may be more tolerable.

Weight reduction should be encouraged in obese patients.

C. PHARMACOTHERAPY

1. General considerations

a. Immunization with influenza vaccine is recommended by the Center for Disease Control and should be administered annually.[17-22] **LE=A, SR=I** Evidence showing benefit with pneumococcal vaccination in COPD patients is controversial. Pneumococcal vaccine is administered once at diagnosis if over age 65; otherwise at diagnosis and at age 65, provided at least 6 years have elapsed since the first dose was administered.[23-30] **LE=B, SR=IIa** Vaccination should be encouraged if the patient does not have contraindications.

b. Need for long-term oxygen therapy should be evaluated. Long-term oxygen therapy has been shown to increase survival in patients with resting hypoxemia and can increase exercise performance and activities of daily living, improve mental functioning, alleviate right heart failure due to cor pulmonale, augment cardiac function, reverse secondary polycythemia, and increase body weight. Patients should be educated on the benefits of oxygen therapy and survival. Refer to VHA guidelines on long-term oxygen therapy.[4]

c. Because of a lower incidence of systemic adverse effects, inhaled bronchodilators are preferred to oral bronchodilators. The amount of inhaled medication deposited in the lung is in direct relation to technique; therefore, providing education on the proper technique in the use of MDI is necessary. (Refer to Appendix 1). The aerosol actuator that comes with a given product should only be used with that product and not used with other aerosol medications. Spacers should be encouraged, to enhance drug delivery. Complicated inhaler regimens should be avoided as patient adherence to

therapy declines. Consider other drug delivery systems (eg. dry powder inhalers) if patient cannot use an MDI with spacer.

d. There is little evidence that nebulizer delivery offers improvement in the management of stable COPD over that of an MDI with spacer. Patients who may benefit from drug delivery via nebulizer are those who have difficulty in using a MDI with a spacer device or other drug delivery systems such as dry powder inhaler devices. The following are examples of patients who may be unable to use a MDI or dry-powder inhaler: those with impaired hand strength or dexterity, visual impairment, mental/cognitive problems, or inability to use an MDI during an acute exacerbation. Nebulizer delivery should be continued only if there is a clear clinical benefit.[31-37] **LE=B, SR=I**

e. Drugs that can exacerbate COPD should be avoided; however, in some situations where the benefits of using the drug outweighs the risk (eg. selective β_1-blockers post MI), the drug may be cautiously administered.[38] It should be noted that patients with COPD have largely been excluded from clinical trials of beta-blocker therapy. If beta-blockers (selective or nonselective) are used, pulmonary function and symptoms must be monitored closely. **LE=C, SR=IIa**

2. Adrenergic agonists

a. Short-acting β_2-adrenergic agonists

1. Available in MDI, dry powder inhalers, nebulizer and oral forms (Refer to Appendix 2
They can improve function and health-related quality of life.

2. Short-acting, selective β_2-agonists are preferred over the non-selective agents because of demonstrated efficacy, rapid action, and selective action on airways. All short-acting agents have similar efficacy and selection could be based on cost.

3. Short-acting β_2-agonists should be used "prn" for the majority of symptomatic patients with COPD.[39-41] **LE=B, SR=1** These agents may also be administered on a scheduled basis for those patients uncontrolled on ipratropium alone.[64-69] Interestingly, one small study has recently shown that ipratropium plus albuterol (using separate inhalers) administered on a scheduled basis is no better than ipratropium plus "prn" albuterol.[43] A larger study confirming these findings is needed.

4. The usual maximum dose is 12 puffs per day for short-acting agents such as albuterol.
The usual single dose of albuterol is 2 puffs. Data concerning added benefit from using more than 2 puffs are variable and was not found in all studies.[44-49]

5. Symptoms may improve without substantial improvement in FEV_1 indicating that continuation of therapy does not depend on routine assessment with spirometry. Patients should be treated with bronchodilators regardless of whether or not there is improvement in FEV1 following bronchodilator administration.

b. Long-acting agent β_2-adrenergic agonists

1. Salmeterol and formoterol are approved for use in COPD.

2. Both salmeterol and formoterol have been compared to ipratropium in 12-week studies.[51, 55, 56] The studies by Mahler[51] and Rennard[55] found no difference between salmeterol and ipratropium in reducing "as needed" β-agonist use, health-related quality of life, patient self-assessment of symptoms (shortness of breath, chest tightness, and cough). Additionally, Rennard found no difference in exacerbation rates and FEV_1 area under the curve (AUC) between ipratropium and salmeterol. Mahler on the other hand found a higher FEV_1 AUC, lower exacerbation rate, and decreased nighttime shortness of breath with salmeterol.

Formoterol and ipratropium increased the 12-hour FEV_1 AUC, though the changes with formoterol were statistically greater than with ipratropium.[56] Formoterol 12mcg achieved a clinically significant improvement in quality of life scores and reduced the number of "as needed" doses of albuterol compared to ipratropium.

In all 3 studies, the patients who had reversibility to albuterol (> 12% and 200ml increase in FEV_1) had a greater response than those who were considered albuterol unresponsive. Also, ipratropium was dosed as 2 puffs qid, which is generally considered a low dose.

Only one study has looked at combining ipratropium with a long-acting β_2-adrenergic agonist versus theβ_2-adrenergic agonist alone .[54] There was added improvement in airway obstruction when salmeterol and ipratropium were combined compared to salmeterol alone. However, the combination did not further improve symptom scores or need for rescue albuterol.

3. Both salmeterol and formoterol have been compared to theophylline .[57-60] Monotherapy with the long-acting β_2-agonists were superior to theophylline monotherapy in improving pulmonary function and reducing rescue medication use.

   The combination of salmeterol and theophylline titrated to a peak concentration of 10-20mcg/mL resulted in improved lung function, decreased symptoms and use of rescue medications, and greater patient satisfaction when compared to either agent given alone. However adverse events were greater in patients receiving theophylline.[60]

4. The role of long-acting β_2-adrenergic agonists in the scheme of COPD therapy needs to be better defined. Potential roles for salmeterol or formoterol include:
   - Patients using ipratropium and are requiring 12 or more puffs a day of a short-acting β_2-agonist
   - Patients who have troublesome, nocturnal dyspnea.
   - Patients requiring maintenance ipratropium but are unable to comply with qid dosing or doses requiring a large number of puffs per day.
   - Should be considered for patients with suboptimal response to scheduled ipratropium and short acting beta agonists before using theophylline.

   Salmeterol or formoterol should only be continued in those patients who experience symptomatic benefit from its addition to their regimens.

5. Because of the slow onset of effect, salmeterol should not be used for acute shortness of breath. Although formoterol has a rapid onset of action similar to albuterol it should not be used to treat acute dyspnea as additional dosing for acute events may result in side effects from the excess β_2-agonist. The short-acting agents should be used for relief of acute symptoms.

6. Use the long-acting β_2-adrenergic agonists cautiously in patients with preexisting cardiac arrhythmias and PO_2 < 60mmHg. One small study showed that the number of isolated supraventricular premature beats and ventricular premature beats were increased with salmeterol and formoterol. Formoterol 24mcg produced more premature beats and reduced serum potassium to a greater extent than salmeterol 50mcg and formoterol 12mcg.[62]

7. Doses higher or more frequent than salmeterol 50mcg bid or formoterol 12mcg bid have not been shown to be more efficacious and in some studies have actually resulted in lower quality of life scores.[50, 57]

c. Oral β_2-agonists

Can be useful for patients who cannot use any inhaled form, although such cases are rare. The risk of systemic adverse reactions is increased significantly with these oral agents (Refer to Appendix 3).

3. Anticholinergics

a. Ipratropium bromide, the prototype anticholinergic bronchodilator, is available as both an MDI and a nebulizer solution (Refer to Appendix 2).

b. Ipratropium bromide and β_2-agonists have similar efficacy. It may cause less severe systemic side effects than the β_2-agonists due to minimal systemic absorption.

c. Ipratropium has a slower onset and longer duration of action than the short-acting β_2-agonists.

c. Use a trial of ipratropium for scheduled dosing in asymptomatic patients with FEV_1 < 50% predicted. At this degree of obstruction, dyspnea is usually present. However, a lack of, or masking of symptoms may be the result of patients avoiding activities and adapting to his/her disability, or the patient may perceive dyspnea as part of the natural aging process. Ipratropium should only be continued in patients where there is evidence of improvement in masked symptoms (eg. the patient begins to engage in some activities that in the past were avoided or associated with dyspnea.) **LE=C, SR=1**

d. Ipratropium should be used in patients who have daily symptoms.[51, 55, 63-69, 71] **LE=A, SR=I**

f. In patients with COPD, ipratropium bromide, at peak effect, typically increases the FEV_1 by 0.15 - 0.35 L.

g. Dosage is 2- 4 puffs four times daily. Some dose-response studies suggest that dosages higher than the manufacturers recommendations might be needed to produce maximal improvement in pulmonary function. Improvement in level of physical functioning can be used to guide therapy.[44, 68-70]

h. Patients with glaucoma should use a spacer to avoid spraying the agent into their eyes.

i. Although ipratropium bromide is minimally absorbed, it should be used with caution in patients with closed angle glaucoma or other conditions potentially worsened by the drug's anticholinergic action.

j. A new drug application for tiotropium, a once daily anticholinergic, is anticipated to be filed with the Food and Drug Administration in the near future.

4. Combination therapy

a. The combination of a β_2-agonist and ipratropium bromide is advised for patients with chronic COPD whose symptoms are inadequately controlled with one agent. The combination of agents in adequate doses may provide a synergistic effect and lessen the risk of adverse effects from higher doses of a single agent.[71-76] **LE=A, SR= I**

b. Combivent® is a product that provides albuterol 90mcg and ipratropium 18mcg per puff, in one metered dose inhaler. This product should not be used as a first-line agent. It may be considered for patients who are well controlled on both individual agents in combination or for those patients requiring ipratropium with scheduled albuterol where adherence to therapy might be improved.

Although Combivent can be safely used as rescue therapy, it is not generally recommended due its' significantly higher cost than that of albuterol.

A combination product for nebulizer use (DuoNeb®) is also available and provides albuterol 2.5mg (as the base) and ipratropium 0.5mg in a single 3ml unit dose vial. Alternatively, a combination can be made by mixing 0.5ml of albuterol solution with 2.5ml of ipratropium solution to provide 2.5mg and 0.5mg respectively.

5. Theophylline

a. Theophylline may be added if response to inhaled bronchodilators is inadequate, however the clinician should first analyze the risk/benefit ratio. It should be continued only for patients who have a beneficial response (eg. improvement in pulmonary function, arterial blood gas symptoms, or exercise performance). [60, 61, 79-83] **LE=B, SR=IIa**

b. Several theophylline preparations are available (Refer to Appendix 4). The slow-release, once-a-day formulations taken at night provide longer control, and may be of benefit for nocturnal dyspnea.

c. Theophylline has a narrow therapeutic index with a high risk of dose-related adverse reactions, especially in older patients. Adverse effects of theophylline include insomnia, anxiety, nausea, vomiting, tremor, palpitations, arrhythmias, delirium, and seizures. Older patients have increased susceptibility to chronic theophylline toxicity.

d. Drug interactions and other factors altering theophylline metabolism are numerous (Refer to Appendix 4).

e. Due to toxicity, the use of theophylline as monotherapy in COPD should be restricted to rare cases where patients cannot adequately administer inhalers or nebulizers.[57, 58, 84-92,] **LE=B, SR=IIa**

f. Dosage should be carefully adjusted to achieve a peak plasma concentration between 5-12mcg/mL. If there is minimal or no response, increase the dose to achieve levels in between 8-15mcg/ml, provided the patient can tolerate the increase. This can be effective in increasing FEV_1 with less risk of adverse effects (Refer to Appendix 4). A peak concentration at the lower end of the range is recommended in elderly patients and in patients who have risk factors for reduced clearance. In general, serum levels for product administered every 12 hours can be obtained 3-7 hours after the morning dose. For the once daily products, the serum level can be obtained 8-12 hours after the dose.[95]

g. Measure the serum theophylline concentration at the start of therapy when steady state is achieved, when pulmonary symptoms changes, acute illness develops, interacting drugs are added or discontinued, non-compliance is suspected, dosage adjustments are made, or immediately after symptoms suggestive of toxicity develop.

6. Corticosteroids

a. Recent evidence has better defined the role of inhaled steroids in the management of COPD. Four large, long-term randomized controlled trials were unable to show that chronic use of inhaled steroids reduces the rate of decline in FEV1. This was demonstrated in patients with all levels of severity of COPD.[97-100]

b. Long-term use of high-dose inhaled steroids in patients with moderate-severe COPD may reduce the frequency or severity of exacerbations, and unscheduled clinic care.[99, 100] One study also showed better health-related quality of life scores for patients receiving inhaled steroids.[100]

c. Patients with mild COPD did not show improvement in exacerbation rates or symptoms when lower doses of inhaled steroids (budesonide 800mcg/day) were used. Whether the use of high-dose inhaled steroids in this group is beneficial is unknown.[97, 98]

d. The decision to institute a steroid trial in patients with COPD should be based on familiarity and experience of the provider. Pulmonary referral may be requested at the provider's discretion.

e. Patients with moderate-severe disease with frequent exacerbations may be considered for an inhaled steroid response trial. The trial should be instituted only when the patient is stable, and is failing maximum bronchodilator therapy. **LE=A, SR=IIa**

f. It is common practice to give a patient a short trial of oral steroids and then attempt a switch to inhaled steroids in those who respond. We do not recommend this practice since the response to an oral steroid trial is not helpful in predicting a response to inhaled steroids.[5, 99, 113]

g. There is no uniform definition or criteria for what constitutes a response to an inhaled steroid trial. According to published data, improvement in spirometry is generally not expected. Although not expected, improvement in spirometry may occur and, on a case by case basis, should be measured to help guide therapy. Outcomes to consider include improvement in symptoms, frequency and severity of exacerbations and related clinic and hospital visits.

h. A six-week trial of high dose inhaled steroids is adequate to evaluate symptomatic response; however, to see improvement in exacerbation rates or severity, a longer trial may be necessary (eg. 6 months). [104-106] If a patient does not respond adequately to the trial, consider tapering and discontinuing the steroid.

i. Although there are no data whether patients with moderate-severe COPD benefit from lower doses of inhaled corticosteroids, lowering the dose may be attempted to see if response is maintained. Use of lower-dose inhaled steroids may lessen the risk of osteoporosis and adrenal suppression.

j. Pulmonary status may deteriorate when inhaled steroids are withdrawn from patients who were receiving maintenance therapy with these agents. [107, 108]

k. Inhaled corticosteroids should be administered with the aid of a spacer, unless contrary to manufacturers specifications. Gargling with water after each oral steroid dose may help prevent oropharyngeal candidiasis. Patients should be monitored for systemic steroid effects resulting from chronic use of high-dose inhaled corticosteroids.

l. Maximum doses of inhaled corticosteroids vary among agents (Refer to Appendix 5).

m. Patients not responding to inhaled steroids may be candidates for a short-term oral steroid trial. Numerous short-term clinical trials (1-3 weeks) have shown that oral corticosteroids will increase FEV1 by 20% or more in approximately 10-20% of patients.[109-110] There are no prospective controlled long-term oral steroid studies in COPD. Two uncontrolled studies demonstrated that long-term oral steroids might decrease the decline in FEV1 in some patients.[111, 112] Given the unproven benefits and the risk of toxicity, oral steroids should be considered in those who cannot take or have not responded to inhaled steroids.

Oral steroid trial

- Since short-term (2-3 weeks) high-dose steroids usually do not produce serious toxicities, the ideal use is to administer the glucocorticoids in a short "burst" (up to 40mg/day for 2-3 weeks of prednisone).
- A positive response includes symptomatic benefit and an increase in FEV1>20%.
- In non-responders, discontinue oral steroid
- It should be remembered that it is not known whether a response to short-term, high-dose oral steroid reliably predicts long-term response
- Combination oral and inhaled steroids may be tried as an oral steroid-sparing measure
- Repeatedly evaluate patients to determine if steroid therapy can be discontinued

For responders, the question remains whether one should continue oral steroids at the lowest possible daily dose or discontinue after the 2-week trial and manage patients with intermittent steroids bursts. One small, randomized VA study looked at whether patients receiving chronic oral steroids can be withdrawn from chronic use and be managed with "on demand use." Although this study had selection bias, was underpowered, and had a high dropout rate, it did provide preliminary evidence that suggests patients can be withdrawn from chronic steroid use and be treated on demand. It should also be noted that patients in this study were receiving concomitant inhaled steroids. [115]

There is insufficient evidence at this time to recommend one single approach. Most practitioners would initially attempt managing patients with intermittent steroid bursts and to reserve chronic low dose steroids for those who have not achieved good control with intermittent treatment.

n. Patients who have received prolonged oral corticosteroid treatment should receive stress doses of steroids during episodes of severe illness or injury. Adrenal insufficiency may persist for up to a year following the discontinuation of chronic steroid therapy. Transfer of a patient from oral to inhaled steroids must be done slowly to avoid risk of adrenal insufficiency. Inhaled corticosteroids, particularly at higher doses may also predispose the patient to adrenal suppression.[116, 117]

o. Adverse effects of oral corticosteroids are numerous, including hypertension, hyperglycemia, weight gain, purpura, mental status changes, depression, glaucoma, cataracts, myopathy, and adrenal suppression. Osteoporosis may occur within 6 months.

p. Long-term use (3 years) of high-dose inhaled steroids in patients with COPD showed a 2% decrease in femoral neck bone density.[100] Another long-term inhaled steroid study using lower doses of inhaled steroids showed no changes in bone density.[98] Patients requiring long-term steroids should be evaluated for risk of osteoporosis and be treated preventively with calcium and vitamin D supplements, and weight-bearing exercise. The biphosphonates alendronate and risendronate are FDA approved for prevention and treatment of steroid-induced osteoporosis. The American College of Rheumatology recommends treatment with alendronate or risedronate in patients receiving at least 3 months of prednisone > 5mg/day.[120] No study has addressed using biphosphonates in patients using long-term inhaled steroids. However, long-term use of inhaled steroids may decrease bone density, particularly when higher doses of the more potent inhaled steroids are used. In such situations, providers might consider obtaining a bone density scan and treat with biphosphonates for those with osteoporosis or osteopenia. Calcitonin and hormone replacement therapy are other options for preventing or treating steroid induced osteoporosis and should be considered where appropriate. Efficacy is mainly limited to preventing bone loss at the lumbar spine. They are less efficacious at preventing or treating bone loss at the femoral neck. [118-120] The risks of long-term steroid treatment should be discussed with the patient.

7. Leukotriene inhibitors

The leukotriene believed to mediate inflammation in COPD is LTB_4 and in asthma is LTD_4. Montelukast and zafirlukast do not inhibit the LTB_4 receptor and are therefore not expected to improve pulmonary function and symptoms of COPD. [5] One single dose study of 16 patients (majority who had >12% increased in FEV_1 with albuterol 400mcg) with COPD found the following rank order improvement in FEV_1: salmeterol 50mcg + zafirlukast 40mg = salmeterol 50mcg > zafirlukast 40mg > placebo. However, there was a subgroup of 7 patients who had a better response with the combination than with salmeterol alone. There are preliminary data that the leukotriene inhibitors may provide some benefit in those who have partially reversible COPD.[122, 155] Larger and longer term studies are needed before these agents can be routinely recommended. If a trial of leukotriene inhibitor therapy is initiated, it should be continued only if pulmonary function, symptoms, exercise tolerance, or well-being improve.

D. MANAGEMENT OF ACUTE EXACERBATIONS

1. Signs and symptoms of acute exacerbation [1-5, 123, 124]

There is no uniform definition of COPD exacerbation or are there standardized validated grading systems for severity. At best, acute exacerbations can be defined as a recent deterioration in the patients' clinical and functional state, beyond that of normal day-to-day variations of their COPD (ERS 1995 and BTS 1997). In general, worsening dyspnea, increased sputum production, and change in character or color of sputum are the most common features associated with an acute exacerbation. Other findings may include:

Increased cough	Fever
Development of or increase in wheezing	Cyanosis
Malaise, fatigue	Use of accessory muscles
Decreased exercise tolerance	Peripheral edema
Increased respiratory rate	Loss of alertness altered mental status
Tachycardia	Worsening airflow obstruction
Shallow breathing	Worsening arterial blood gases

The most common precipitating event is acute bronchitis; however the differential diagnosis includes pneumonia, pneumothorax, heart failure, pulmonary edema, and pulmonary embolism.

A severe exacerbation is suggested by the following: mental status changes, dyspnea at rest, respiratory rate >25/min, heart rate >110/min, cyanosis, accessory muscle use, pO_2 < 60mmHg on room air. Patients presenting with a severe exacerbation, should be referred to the emergency department.

2. **Bronchodilators**

a. Short-acting inhaled $beta_2$-agonists such as albuterol, are the bronchodilators of choice to treat COPD exacerbations. These agents can be beneficial by improving FEV_1 and dyspnea.[125-127] **LE=B, SR=1**

b. Although the maximally effective dose in COPD exacerbation is not known, there are limited data suggesting that 3-4 puffs produces significant bronchodilation. The duration of action is shorter during an acute exacerbation; therefore, more frequent administration (q 1-3 hours) may be necessary. The 1995 ATS Consensus Statement concludes that dosages for severe exacerbations may be as high as 6-8 puffs every ½-2 hours. As symptoms improve, the frequency and or dose can be reduced. Patients who have received instruction on home management of exacerbations should contact the provider if not responding to initial measures.

c. Higher doses of these agents increase the risk of adverse reactions, such as tremor and cardiac arrhythmias. Higher doses of inhaled $beta_2$-agonists should be used cautiously in patients with known coronary artery disease, arrhythmias, or left ventricular dysfunction. An alternative therapy is to be to combine inhaled ipratropium at higher than usual doses with the β_2-agonist at moderate doses.

d. If the patient is not obtaining the benefit from the MDI with spacer, the β_2-agonist can be given via nebulizer (eg. albuterol 2.5mg q 2-4 hours). Studies showing equivalency between MDI and nebulized delivery were done primarily in the emergency department or hospital setting.[129-131] **LE=A, SR=IIa**

e. Inhaled ipratropium can be used to treat acute exacerbations of COPD. As a single agent, its effect on spirometry is equal to that of inhaled β_2-agonists. While ipratropium can be used to treat exacerbations, its slower onset of action makes $beta_2$-agonists the preferred drug during acute exacerbations.[125, 126, 132] **LE= B, SR=I**

f. Ipratropium may be dosed at 3-4 puffs q3-4 hours. The ATS suggests that doses of 6-8 puffs q 3-4 hours can be used in severe cases; although, a dose-response relationship has not been determined for higher doses of ipratropium in COPD exacerbation.

g. Ipratropium 0.5mg q 2-8 hours via nebulizer can be given to patients who cannot use an MDI with spacer.

h. Combination beta-agonist and anticholinergic has been evaluated in 9 studies; 7 assessed short-term outcomes[125, 126, 132, 134-137], 1 looked at outcomes at 24 hours[133], and 1 inpatient study assessed outcomes up to the time of discharge[156]. Six of the short-term, the 24-hour, and the inpatient study showed no additional benefit in pulmonary function with the combination. These studies were relatively small, so a difference between treatment groups may have been missed. At this time, there is insufficient evidence that the combination provides any short-term advantage over use of single agents. **LE= B, SR=I**

3. **Corticosteroids**

a. Recent data has shown that steroid administration improves pulmonary function and decreases relapse rate in patients with acute exacerbations requiring hospitalization.

The dosing and duration of treatment varied from study to study, making it difficult to recommend a specific regimen. An example of a reasonable regimen is IV methylprednisolone at 0.5mg/kg q 6 hours x 72 hours followed by oral prednisone, for an additional 7-10 days.[138-142] LE=**A, SR=IIa**

In the VA based SCCOPE trial, therapy lasting longer than 2 weeks was not found to be more beneficial than a 2-week regimen.[141]

In the SCCOPE trial, hyperglycemia warranting treatment occurred in 15% of patients receiving steroids compared to 4% receiving placebo. [141]

b. There is a paucity of data concerning steroid use for managing acute exacerbations in the outpatient or emergency room setting. It is unclear whether all acute exacerbations merit treatment with systemic corticosteroids. However, the following patients should be considered for systemic steroid treatment: patients on maintenance oral or inhaled steroids; patients who have recently stopped oral steroids; patients who have had a prior response to oral steroids; patients with a low oxygen saturation ($\leq$ 90%); patients with PEFR $\leq$ 100L/min; or patients not responding to initial bronchodilator therapy. **LE=C, SR=IIa**

One study showed that a single dose of IV methylprednisolone 100mg did not improve FEV_1 or rate of hospitalization over that of placebo. Thompson found that a 9-day course of oral prednisone, administered in a tapering fashion, improved FEV_1, PEF, pO_2, and decreased relapse rates when compared to placebo. Bullard found that hydrocortisone 100mg IV q 4 hours resulted in greater increases in peak flow, FEV_1, and ED discharges than placebo.[143-145] **LE=A, SR=IIa**

The dose, duration, and tapering of therapy for a course of oral steroids remains to be established. Prednisone 0.6 - 0.8mg/kg/day for 7-14 days is often used in clinical practice. No study has looked at whether tapering of the steroid dose is necessary; however, many clinicians include a taper as part of the treatment course. **LE=C, SR=IIb**

Upon completion of a steroid course, the patient must be monitored for potential relapse.

c. Patients already on higher doses of steroids (eg. prednisone 40-60mg) that have not responded to intensive bronchodilator therapy should be referred for specialist consultation on an emergent basis or for hospital admission.

4. **Antibiotic Therapy**

a. Antibiotic therapy is not indicated for all acute exacerbations of COPD since viruses or environmental exposures can also result in acute exacerbation.[157]

b. If the exacerbation is associated with changes in sputum (quality, volume, or color), and increased dyspnea, cough or fever, treatment with antibiotics is reasonable.[147-152] **LE=B, SR=I** Presence of an infiltrate on chest radiograph suggests pneumonia; the patient should be treated with antibiotics as deemed appropriate.

c. Older patients or those with severe underlying lung dysfunction are most likely to benefit from antibiotic therapy.[147-149, 152] However, one retrospective review at Veterans Affairs Medical Center found that patients treated with antibiotics had a lower relapse rate than those who did not receive antibiotics and that severity of the exacerbation or the underlying disease was not predictive of relapse.[151]

d. The most commonly isolated bacteria include, *Haemophilus influenza, Moraxella catarrhalis*, and *Streptococcus pneumoniae*.

e. Sputum cultures, carefully obtained, may be helpful, especially in patients who have failed to respond to initial empiric antimicrobial therapy. Choice of antibiotic should consider local sensitivity patterns and patient allergies. In areas where resistance is not a problem, established antibiotics, such as amoxicillin, doxycycline or trimethoprim/sulfamethoxazole, may be used. One VA study conducted in San Antonio, found a higher relapse rate in patients receiving amoxicillin.[151] The optimal duration of treatment is unknown; however, many clinicians choose a 7-14 day course.

f. The newer antibiotics, such as quinolones, amoxicillin-clavulanate, 2nd or 3rd generation oral cephalosporins or the newer macrolides should be reserved for special situations: treatment failure with conventional agents, recent hospitalizations, nursing home residents, advanced COPD, pneumonia, or bacterial isolate resistant to older established antibiotics.

5. **Theophylline**

a. Due to minimal evidence of efficacy and potential risk of toxicity, the role of theophylline in acute COPD exacerbation is questionable. In general, if the patient is not on theophylline, there is no need to start it in the setting of an acute exacerbation.[153, 154] **LE=B, SR=IIb**

b. If the patient is already on theophylline, adjust the dosage, as necessary, to achieve a serum concentration of 5-12 mcg/mL. Keep in mind that certain factors such as antibiotics or fever can alter theophylline concentrations. (Refer to Appendix 4)

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Some useful websites for patient education

http://www.nih.gov/health/consumer/conkey.htm
http://www.lungusa.org for patient education
www.surgeongeneral.gov/tobacco/default/htm

Appendix 1. A Method for the Correct Use of Metered - Dose Inhalers (MDI)

- Remove the cap and shake the inhaler thoroughly
- Exhale normally
- Hold the inhaler upright
- Place the mouthpiece ¾ inch (approximately two fingers) in front of the lips. For some patients, it may be preferable to place the mouthpiece between the lips making sure the teeth and tongue are out of the way
- Press down on the inhaler while inhaling slowly and deeply
- Hold the breath for 10 seconds, if possible
- Breath out slowly through nose or pursed lips
- Take one puff at a time. Pause at least 20 seconds before the next inhalation

Only 10 - 15 % of the spray reaches the lungs
If technique is inadequate use a spacer device; only a minority of users perform correct technique; emphasize and monitor compliance with the use of MDIs

Appendix 2. Dosages of Inhaled Bronchodilators in COPD[a]

DRUG	MDI DOSE	USUAL MDI PUFFS[b]	MAXIMUM DOSES[c]	NEBULIZER SOLN AVAILABLE	PRECAUTIONS IN DRUG USE
Sympathomimetics					• Use spacers to enhance delivery and reduce systemic effects • Instruct patient on maximum # of puffs per day and on # allowed during an exacerbation (e.g. 12-24 over 3 - 4h) before additional intervention is required
Albuterol[d]	0.09 mg	1-2 q 4-6 h	12 puffs/day	Yes	
Bitolterol	0.37 mg	2 q 8 h	12 puffs/day	Yes	
Metaproterenol	0.65 mg	2-3 q 3-4 h	12 puffs/day	Yes	
Pirbuterol	0.20 mg	1-2 q 4-6 h	12 puffs/day	No	
Salmeterol[e]	0.02 mg	2 q 12h	4puffs/day	No	
Anticholinergic Agents Ipratropium	0.018 mg	2 - 3 q 6 h	12 puffs/day	Yes	• Caution patient that onset of effect is relatively slow • Monitor for side effects (e.g. tachycardia, dry mouth, glaucoma, bladder neck obstruction or prostatism)
Combination Products Albuterol + ipratropium	0.09mg/ 0.018mg	2-3 q 6 h	12 puffs/day	Yes	• Same warnings as above for ipratropium • May be used in patients well-controlled on each individual agent
BREATH ACTUATED DRY POWER INHALED BRONCHODILATORS					
Salmeterol 50mcg Diskus[e]	Inhaled dry powder in blister pack		50mcg q 12 h		
Formoterol 12mcg	Inhaled dry powder capsules		12mcg q 12 h		
Albuterol 200mcg Rotocaops	Inhaled dry powder capsules		200-400mcg q 4-6hours		

[a] Adapted from ATS statement; Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc.,1996.

[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 a chlorofluorhydrocarbon-free aerosol (CFC-free)

[e] Also available in the following combination products: fluticasone 100mcg/salmeterol 50mcg; fluticasone 250mcg/salmeterol 50mcg; fluticasone 500mcg/salmeterol 50mcg

Appendix 3. Dosages of Oral β-adrenergic agonists in COPD

DRUG	ORAL DOSE	PRECAUTIONS
Albuterol Immediate release Sustained release	2 - 4 mg tid -qid, 4 - 8 mg q 12 h	• 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 β_2-agonists
Metaproterenol	10 mg bid-tid	
Terbutaline	5 mg tid	

Adapted from ATS statement and Bronchodilators. In: Hebel SK, ed. Facts and Comparisons, St. Louis: Facts and Comparisons Inc., 1994:173a- 177b.

Appendix 4. Theophylline

Several theophylline products will be going off the market: Slo-Bid, Slo-phyllin, Theo-Dur, Theolair-SR, and Uni-Dur. Companies will continue to ship product until supplies have been depleted which is expected to occur by year's end 2001.

Theophylline Preparations [a]

FORMULATION	DOSING INTERVAL	COMMENTS
Theophylline (various manufacturers) Generic preparations available in liquid, capsule, and tablet forms	3-4 times/day	• Complete absorption occurs in the presence or absence of food • Immediate release formulations should be avoided due to short half-life, especially in smokers
theophylline extended-release (various manufacturers) 100, 200, 300mg tablets 100, 125, 200, 300 capsules	2 - 3 times/day	• Complete absorption occurs in the presence or absence of food • Contents must be swallowed without chewing • Scored tablets can be split without affecting absorption characteristics • AB rated products are recommended[b]
Uniphyl® Tablets 400, 600 mg Theo-24® Capsules 100, 200, 300, 400 mg	Once daily	• Use in patients non-compliant with bid regimens • Caution: fluctuations may occur in serum concentrations • Incomplete absorption occurs when taken after an overnight fast • More complete absorption occurs when taken after food or in the evening

[a] Hendeles L, Massanari M, Weinberger M. Theophylline. In: Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics: Principles of Therapeutic drug monitoring. 3rd ed. Vancouver: Applied Therapeutics Inc., 1992:13-1 - 13-30.

[b] AB rating - considered as therapeutically equivalent by the FDA.

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,[c] cor pulmonale, elderly (> 60 yrs.), hepatic insufficiency[b] (cirrhosis, acute hepatitis, cholestasis), fever (> 24 hrs.)	charcoal-broiled food; low carbohydrate, high protein diet; smoking (tobacco or marijuana); phenobarbital; phenytoin; rifampin, carbamazepine; isoniazid; moricizine

[a] Adapted from Weinberger M, Hendeles L. Drug therapy: Theophylline in asthma. N Eng J Med 1996;334:1380-1388 and Hendeles L, Jenkins J, Temple R. Revised FDA labeling guideline for theophylline oral dosage forms. Pharmacotherapy 1995;15(4):409-427. **This list is not intended to be inclusive of all potential drug interactions.**

[b] Theophylline clearance has been decreased by 50% or more

Dosing Guidelines

	Starting dose		Maintenance dose
Adults (16-60 years) Without Risk Factors for Impaired Clearance	Initial dose 400mg/day	If using prompt release tablets, divide daily dose q6-8hrs Dosing may also be initiated with the 12-hour extended release products In general, once daily products (eg. Uniphyl or Theo-24) should not be used when initiating theophylline	If serum concentration < 5mcg/ml and symptoms are not controlled, increase daily dose by 25% If serum concentration 5-12mcg/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 15mcg/ml
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		

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.

Appendix 5. Dosages of Inhaled Steroids in COPD[a-b]

Inhaled steroid	Dosage forms	Usual dosing interval	Low dose mcg/day	Medium dose mcg/day	High dose mcg/day	Maximum dose per manufacturer
Flunisolide 250mcg	MDI	Q 12h	500-1000 (2-4 puffs)	1000-2000 (4-8 puffs)	>2000 (> 8 puffs)	2000
Triamcinolone 100mcg	MDI with built-in spacer	Q 6-8h or Q 12h	400-1000 (4-10 puffs)	1000-2000 (10-20 puffs)	>2000 (>20 puffs)	1600
Beclomethasone 42mcg[c]	MDI	Q 6-8h or Q 12h	168-504	504-840	>840	840
Budesonide 200mcg	DPI	Q 12h	200-600 (1-3 inhalations)	600-1000 (3-5 inhalations)	>1000 (> 5 inhalations)	1600
Fluticasone[d] (MDI) 44mcg 110mcg 220mcg (DPI) 50mcg, 100mcg, 250mcg	MDI, DPI (blister packs)	Q 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

[a] Not approved by the FDA for COPD

[b] Dose per National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 2:Guidelines for the Diagnosis and Management of Asthma

[c] Also available in a chlorofluorhydrocarbon-free aerosol (CFC-free)

[d] Also available in the following combination products: fluticasone 100mcg/salmeterol 50mcg; fluticasone 250mcg/salmeterol 50mcg; fluticasone 500mcg/salmeterol 50mcg

Appendix 6. Selected Costs for COPD Drug Therapy (2002) based on the federal supply schedule[a]

DRUG	USUAL DOSE[b]	PUFFS/ MDI	COST/INHALER	COST/MONTH
Inhaled Adrenergic Agents				
Albuterol 90mcg	1-2 puffs q 4-6 h	200	$ 1.75	2 inhalers/month = $3.50
Bitolterol	2 puffs q 4-8 h	300	$ 7.60	1 inhaler/month = $ 7.60
Metaproterenol	1-3 puffs q 3-4 h	200	$ 11.88	2 inhalers/month = $23.76
Pirbuterol	1-2 puffs q 4-6 h	300	$ 17.58	1 inhaler/month = $17.58
Salmeterol 25mcg	2 puffs q 12 h	120	$ 42.72	1 inhaler/month = $42.72
Salmeterol 50mcg Diskus	1 inhalation q12h	60 doses	$45.32	1 Diskus/month = $45.32
Formoterol 12mcg	1 inhalation q 12h	60 doses	$36.25	1 Aerolizer/month = $36.25
Anticholinergic Agent				
Ipratropium	2-3 puffs q 6 h	200	$ 19.59	2 inhalers/month = $39.18
Combination Products				
Albuterol/ipratropium	2 puffs q 6 h	200	$ 22.47	2 inhalers/month = $ 44.94
Salmeterol 50mcg/fluticasone 250mg Diskus	1 inhalation 12 h	60 doses	$80.54	1 Diskus/month = $80.54
Inhaled Corticosteroids				
Beclomethasone 42mcg	2-4 puffs q 6 h	200	$ 21.00	2 inhalers/month = $42.00
Budesonide	1-2 puffs q 12 h	200	$ 70.91	1 inhaler/month = $70.91
Flunisolide	2-4 puffs q 12 h	100	$ 12.60	2 inhalers/month = $ 25.20
Fluticasone 110mcg	1-2 puffs q 12 h	120	$39.60	1 inhaler/month =$39.60
Fluticasone 220 mcg	1-2 puffs q 12 h	120	$ 60.10	1 inhaler/month = $60.10
Triamcinolone	2-4 puffs q 6 h	240	$ 24.27	2 inhalers/month = $48.54

DRUG	USUAL DOSE[b]	COST/MONTH
Oral Adrenergic Agents		
Albuterol	IR: 2-4 mg tid-qid	2 mg tablets: $1.35 - 1.80 4 mg tablets: $ 2.70 – 3.60
	SR: 4 mg q 12 h	$ 20.88
Metaproterenol	10 mg tid - qid	$ 14.69 - 19.58
Terbutaline	5 mg tid	$ 27.00
Oral Corticosteroid		
Prednisone	Up to 40 mg qd	5 mg tablets: $ 1.48
Theophylline Preparations		
Theo-24	400mg qd	$10.56
Uniphyl®	400 mg qd	$ 2.56

[a] Please refer to the PBM website at www.vapbm.org for current pricing

[b] Usual doses; does not reflect equivalent doses