Medical Advisory Panel for the
Pharmacy Benefits Management
Strategic Healthcare Group

The Pharmacologic Management of Chronic Obstructive Pulmonary Disease

Department of Veterans Affairs
Veterans Health Administration
Publication No. 99-0012
Updated June 1999

Department of
Veterans Affairs

Memorandum

Date: June 10, 1999

From: Under Secretary for Health (10)

Subj: Pharmacologic (Drug) Treatment Guidelines Update

To: VISN Directors, VISN Clinical Managers, Medical Center Directors,
Chiefs of Staff and Patient Care Staffs

1. To date, VHA has issued eleven drug treatment guidelines for common diagnoses associated with our patient population, and other guidelines will follow. Please find the attached updated drug treatment guideline for the ***Pharmacologic Management of Chronic Obstructive Pulmonary Disease.***

2. The Medical Advisory Panel of VHA's Pharmacy Benefits Management Strategic Healthcare Group consulted on the development and refinement of this guideline. This guideline and those which will follow in future months, are intended to promote consistent, quality care for patients throughout the VHA health care system.

3. The guidelines are based on nationally recognized treatment guidelines, current literature and expert opinion from clinicians across the VA system. The guidelines are dynamic and will be revised as new clinical data becomes available. Also, the guidelines are not intended to interfere with clinical judgement that might dictate deviation under special circumstances. Rather, they are intended to assist practitioners in providing consistent, high quality care.

4. I commend the efforts put forth in the development of these guidelines and know from the many comments received from throughout the VA that they are a welcome tool for both practitioners and managers. I strongly encourage their utilization and will closely follow their implementation, as well as the outcomes associated with their use. They constitute a significant advancement in VHA's evolution toward a truly integrated health care delivery system.

Kenneth W. Kizer, M.D., M.P.H.

Attachment

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

PBM Publication No. 99-0012; June 1999
Updated versions can be found @ www.vapbm.org or vaww.pbm.med.va.gov

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.

The MAP comprises practicing VA physicians from facilities across the nation:

Peter A. Glassman, M.B.B.S., M.Sc.
Chairman, Medical Advisory Panel
Staff Internist , Department of Medicine
VAMC West Los Angeles, CA.
Assistant Professor of Medicine,
University of California, Los Angeles

Howard R. Bromley, M.D.
Chief, Anesthesiology
VAMC Charleston
Associate Professor of Anesthesiology
Critical Care and Pain Management

Barry Cusack, M.D.
Chief, Geriatric Section
VAMC Boise, ID.
Associate Professor of Medicine
Division of Gerontology &
Geriatric Medicine, School of Medicine
University of Washington

Gregory Dalack, M.D.
Acting Chief, Psychiatry Service
VAMC Ann Arbor
Assistant Professor of Psychiatry
University of Michigan

LTC John R. Downs, M.D.
DoD Pharmacoeconomics Center
Ft. Sam Houston, Texas

Michael Ganz, M.D.
Chief, Nephrology
VAMC Cleveland
Associate Professor in Medicine
Case Western Reserve University

C.B. Good, M.D., M.P.H.
Staff Physician, Department of Medicine
VAMC Pittsburgh, PA.
Associate Professor of Medicine,
University of Pittsburgh

Patricia S. Hlavin, M.D., MS.
Director Urgent Care Center/Emergency Room
Director, FIRM Blue General Medicine Clinics
VAMC San Diego, CA.
Assistant Clinical Professor of Medicine,
University of California, San Diego

Donald Holleman, M.D.
Staff physician, Primary Care
VAMC Lexington
Associate Professor of Medicine
University of Kentucky

William Korchik, M.D.
Director, Extended Care Center
Medical Director, Adult Day Health Care
VAMC Minneapolis, MN.
Assistant Professor of Medicine,
University of Minnesota

John Pope, M.D.
Director, Mental Health
Colmery-O'Neil VAMC
Instructor of Psychopharmacology
Karl Menninger School of Psychiatry

Alexander Shepherd, M.D.
Professor of Medicine and Pharmacology
University of Texas Health Science Center
Dept of Pharmacology & Medicine
San Antonio, Tx

PBM Publication No. 99-0012; June 1999
Updated versions can be found @ www.vapbm.org or vaww.pbm.med.va.gov

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.

John E. Ogden, R.Ph., MS, FASHP
Chief Consultant, PBM SHG
VA Headquarters

Andrew Muniz, R.Ph., MS, FASHP
Deputy Chief Consultant, PBM SHG
VA Headquarters

Michael Valentino, R.Ph., MHSA
Associate Chief Consultant, PBM SHG

Muriel Burk, Pharm.D.
Clinical Pharmacy Specialist

Christine Chandler, Pharm.D.
Clinical Pharmacy Specialist

Fran Cunningham, Pharm.D.
Program Manager for
Pharmacoepidemiologic Research

Elaine M. Furmaga, Pharm D.
Clinical Specialist

Lori Golterman, Pharm.D.
Clinical Pharmacy Specialist

Cathy Kelley, Pharm.D.
Clinical Pharmacy Specialist

Deborah Khachikian, Pharm.D.
Clinical Pharmacy Specialist

Kathryn Tortorice, Pharm.D., BCPS
Clinical Pharmacy Specialist

PBM Publication No. 99-0012; June 1999
Updated versions can be found @ www.vapbm.org or vaww.pbm.med.va.gov

Development of the Guidelines

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 VA population. Draft guidelines are sent to the field for comments prior to being finalized.

Use of the Guidelines

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 primary care practices but are directed to providers at all levels of training. The guidelines also serve as a basis for monitoring local, regional and national patterns of pharmacologic care.

Guidelines give a suggested course of action based upon the typical patient with typical presentation of the target disorder. Whether any guideline suggestions are appropriate for an individual patient is a matter of clinical judgement.

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 Drug and Pharmaceutical Product Management (DPPM) home page at http://www.dppm.med.va.gov

Tables of Evidence

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	B	C

Primary evidence	Large, randomized trials with clear-cut results (low risk of error)	Small, randomized trials with uncertain results (moderate to high risk of error)	Nonrandomized, contemporaneous controls; nonrandomized, historical and expert opinions; uncontrolled studies, case series, and expert opinions
Secondary evidence	Other clinical studies	Clinical studies related to topic	Clinical studies unrelated to topic

Strength of recommendation

1 - Usually indicated, always acceptable and considered useful and effective.

2a – Acceptable, of uncertain efficacy and may be controversial. May be helpful, not likely to be harmful.

2b – Acceptable, of uncertain efficacy and may be controversial. Not well established by evidence, can be helpful and probably not harmful.

3 – 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.

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)

Participant List

Deborah Khachikian, Pharm.D (PBM co-author) Clinical Pharmacy Specialist Pharmacy Benefits Management	Elaine Furmaga, Pharm.D. (PBM reviewer) Clinical Pharmacy Specialist Pharmacy Benefits Management
Barry Cusack, M.D. (MAP co-author) Chief, Geriatric Section VAMC Boise, ID	Lisa R. Gillen, Pharm.D. (field reviewer) Pharmacy Practice Resident VAMC Kansas City, MO

Associate Professor of Medicine Division of Gerontology & Geriatric Medicine School of Medicine, University of Washington	Chester B. Good, M.D. (MAP reviewer) Chair-elect MAP Internal medicine VAMC Pittsburg Associate Professor of Medicine, University of Pittsburg
Peter Almenoff, M.D. (field reviewer) National Program Director, Pulmonary/Critical Care Medicine VA Headquarters Director of Critical Care Services VAMC Kansas City	Peter Glassman, M.B.B.S., M.Sc. (MAP reviewer) Chairman, Medical Advisory Panel Staff Internist, Dept. of Medicine VAMC West Los Angeles, CA Assistant Professor of Medicine, UCLA
Antonio Anzueto, M.D. (field reviewer) Associate Professor of Medicine San Antonio VAMC San Antonio, Tx	Martin Heyworth, M.D. (field reviewer) Chief, Medical Service Professor of Internal Medicine Fargo VAMROC
Bruce Buchanan, M.D. (field reviewer) Physician Spokane VAMC Spokane, WA	Donald Holleman, M.D. (MAP reviewer) Staff physician, Primary Care VAMC Lexington Associate Professor of Medicine- University of Kentucky
Muriel Burk, Pharm.D. (PBM reviewer) Clinical Pharmacy Specialist Pharmacy Benefits Management	Maqual Infranca-Graham Pharm.D. (field reviewer) Clinical Pharmacist VAMC Kansas City Assistant Professor, School of Pharmacy University of Missouri-Kansas City
Christine Chandler, Pharm.D. (PBM reviewer) Clinical Pharmacy Specialist Pharmacy Benefits Management	S. Lakshminarayan, M.D. (field reviewer) Chief, Pulmonary Critical Care Medicine VA Puget Sound Health Care System Seattle, WA
Richard E. Crowell, M.D. (field reviewer) Chief, Pulmonary and Critical Care Associate Professor of Medicine Albuquerque, NM	York E. Miller, M.D. (field reviewer) Assistant Chief, Respiratory Denver VAMC Denver, CO
Gregory Dalack, M.D. (MAP reviewer) Acting Chief, Psychiatry Service Assistant Professor of Psychiatry University of Michigan	Thomas J. Prendergast, M.D. (field reviewer) Chief, Pulmonary Section White River Junction VAMROC White River Junction, VT
Burton Dickey, M.D. (field reviewer) Chief, Pulmonary and Critical Care Houston VAMC	Kathryn Tortorice, Pharm.D., BCPS (PBM reviewer) Clinical Pharrmacy Specialist Pharmacy Benefits Management
LTC John R. Downs, M.D., USAF, MC (MAP reviewer) Air Force Medical Consultant DoD Pharmacoeconomics Center Ft. Sam Houston, Texas	Frank Turner, M.D. (field reviewer) Pulmonologist/Primary Care Provider VA Roseburg Healthcare System, Oregon
James Finley, M.D., Ph.D. (field reviewer) Director of Respiratory Therapy and MICU/CCU Division of Pulmonary Medicine VA Healthcare System of Ohio, Cleveland	Ken Yoneda, M.D. (field reviewer) Assistant Chief, Pulmonary Northern California VA Healthcare System Martinez, CA

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 (Refer to Algorithms 1 and 2)

   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.

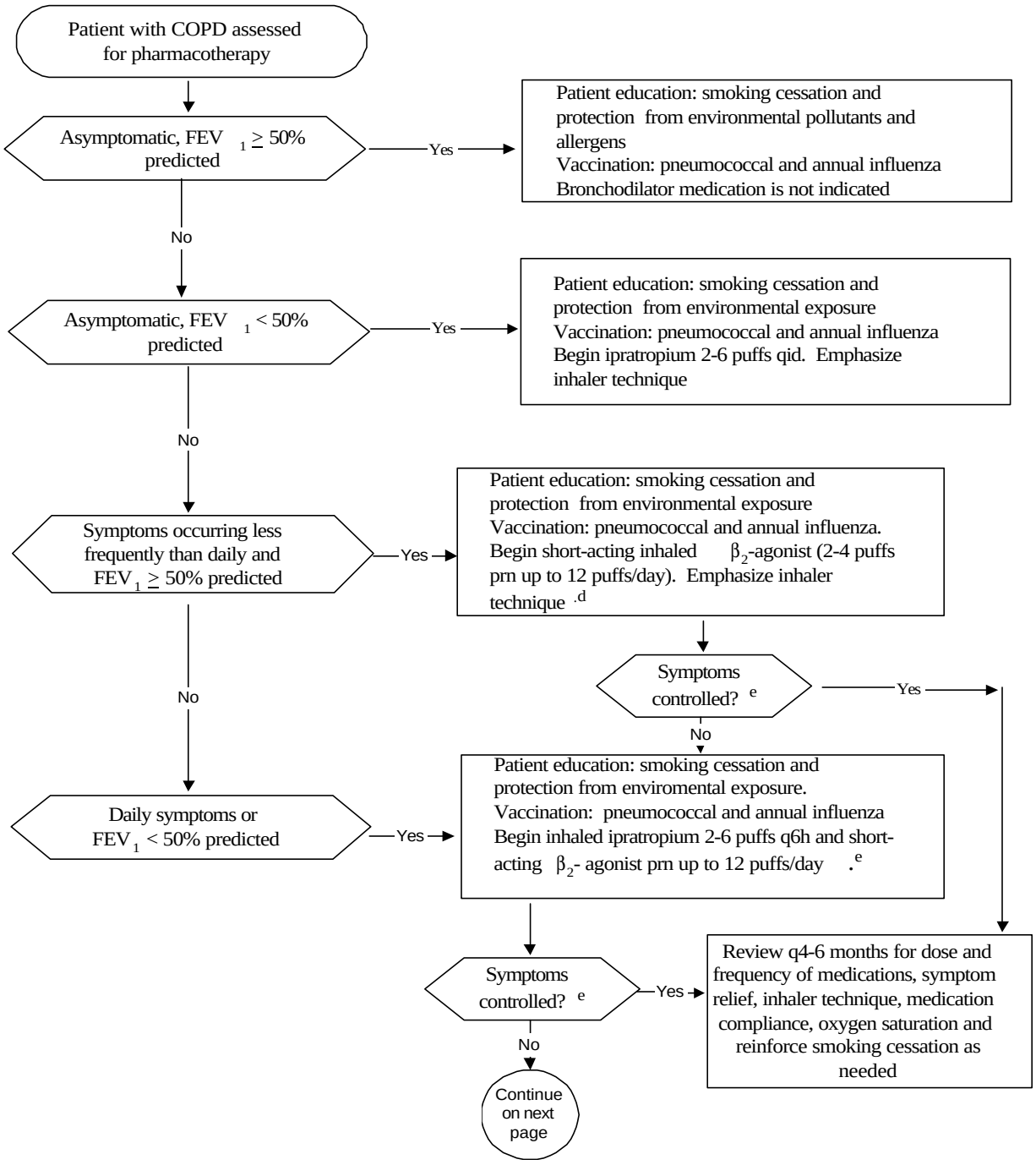
   B. The short-acting β_2-adrenergic agonist metered-dose inhalers (MDIs) such as albuterol and metaproterenol, are generally effective agents for either as-needed (prn) or regular administration. Salmeterol, a long-acting agent, is FDA approved for use in COPD. Its place in therapy is not well defined at this time. Salmeterol may be beneficial for patients with significant nocturnal dyspnea or for those requiring more than 12 inhalations per day of short-acting β_2-adrenergic agonists.

   C. 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.

   D. The use of long-term corticosteroids for COPD patients remains controversial Less than 20-25% of patients benefit. In view of corticosteroids' controversial role in COPD, we recommend their use only if objective benefit is documented by a short-term trial in stable patients not adequately controlled on bronchodilator therapy.

PBM Publication No. 99-0012; June 1999
Updated versions can be found @ www.vapbm.org or vaww.pbm.med.va.gov

Algorithm 1.[a,b,c] Outpatient Pharmacotherapy of COPD



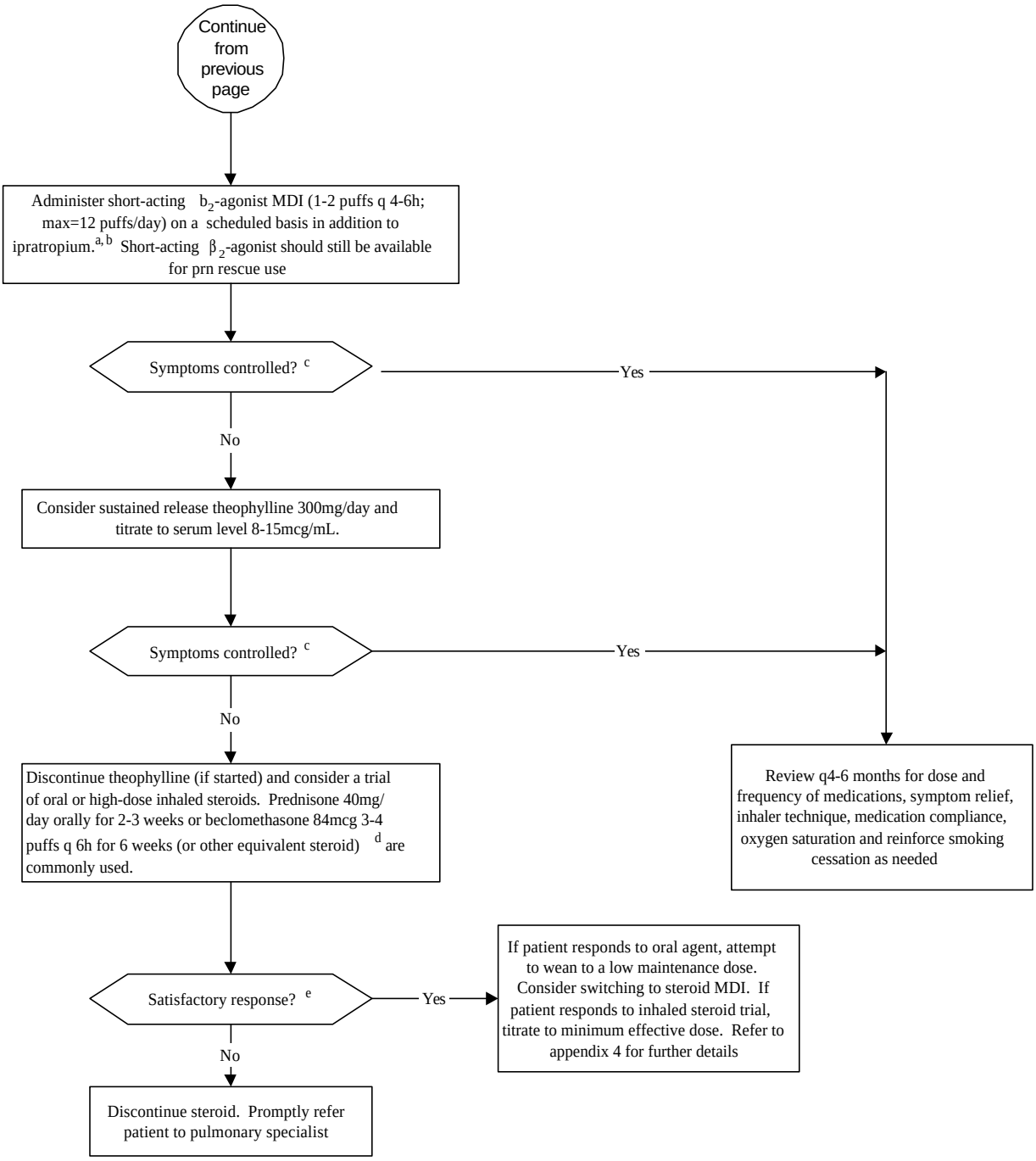
[a] Adapted from ATS statement, British Thoracic Society statement, and VHA Clinical Practice Guideline for COPD/asthma www.va.gov/health/pulmonary/clin_prac/content.htm

[b] This algorithm shows the 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

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

[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 algorithm



[a] 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

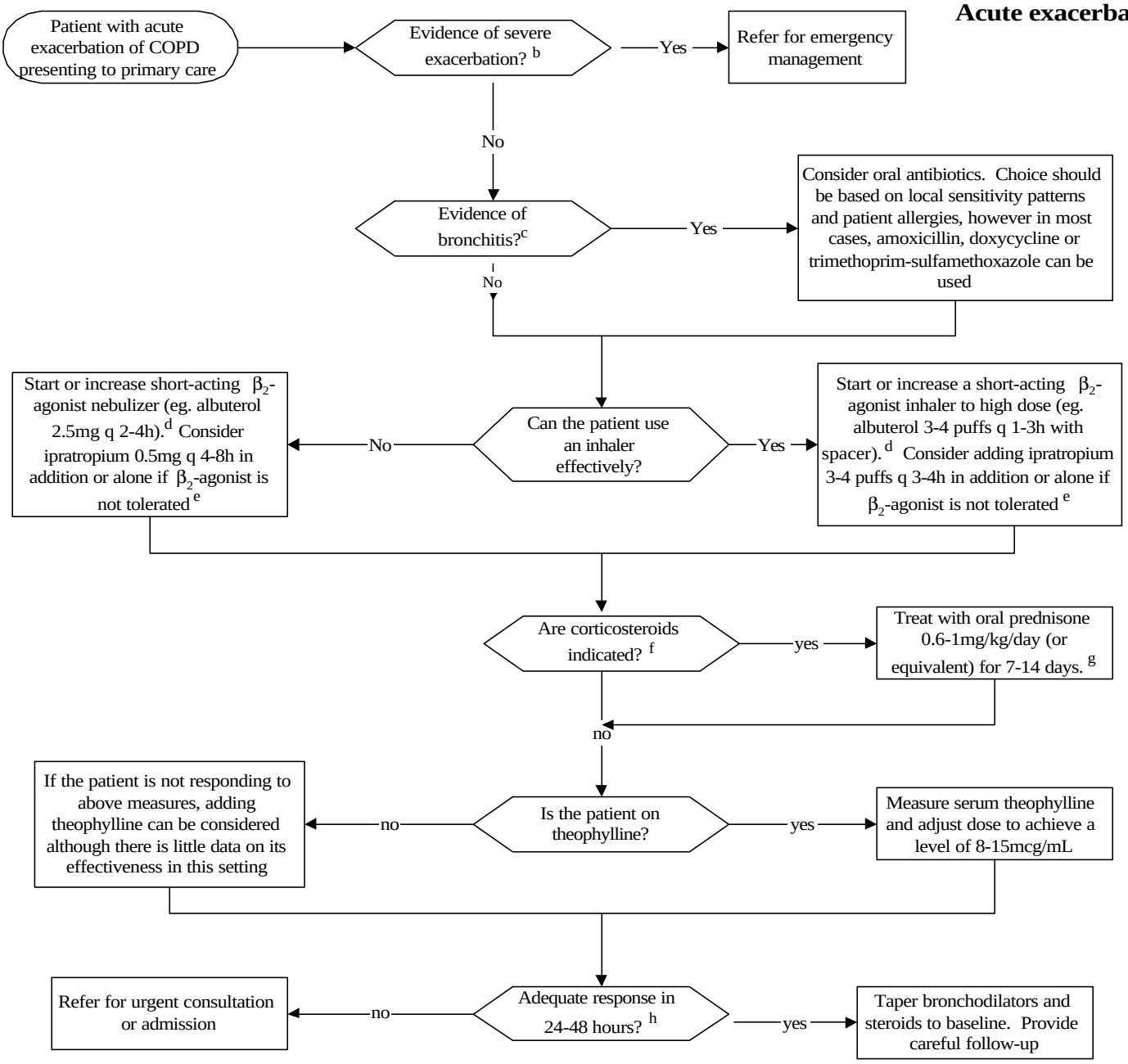
[b] Salmeterol may be considered in those unable to comply with frequent short-acting β_2-agonists or in patients with nocturnal dyspnea

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

[d] Use of inhaled corticosteroids for this purpose is less well documented than oral corticosteroids

[e] As determined by an improvement in FEV1 > 20% predicted and symptomatic benefit

Algorithm 2[a]
Acute exacerbation



[a] Adapted from the ATS guidelines, BTS guidelines, and VHA guidelines for COPD/Asthma www.va.gov/health/pulmonary/clin_prac/content.htm

[b] Loss of alertness plus at least 2 of the following: dyspnea at rest, respiratory rate> 25/min, heart rate >110/min, increased cyanosis, use of accessory muscles

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

[d] Maximum dosages of short-acting β_2-agonists are 6-8 puffs q 1/2-2h (MDI) and a dosing frequency of q 1/2-2 h for nebulizers for severe exacerbation; excessive increase in heart rate may limit frequency of dosing

[e] Maximum dosage of ipratropium is 6-8 puffs q 3-4h with a spacer. There is no evidence that addition of ipratropium provides added clinical benefit

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

[g] A short-term response to corticosteroids in COPD exacerbation does not imply long-term benefit

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

PBM Publication No. 99-0012; June 1999
Updated versions can be found @ www.vapbm.org or vaww.pbm.med.va.gov

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 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.

C. NATURAL HISTORY

1. Age, FEV_1, P_{O_2}, P_{CO_2} and cor pulmonale are prognostic factors.

2. Those with a reversible component ($\geq$ 15% increase in FEV_1 with inhaled β_2-agonist) may have a better prognosis.

III. PATIENT EVALUATION

CLINICAL FEATURES

1. History

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

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

c. Occupational/environmental exposure.

2. Physical Examination

a. The sensitivity of physical examination is low for diagnosing mild or moderate COPD.

b. Physical signs of COPD include wheezing, prolonged forced expiratory time, decreased breath sounds, decreased ribcage expansion, decreased 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.

IV. TESTS TO GUIDE PHARMACOLOGIC MANAGEMENT

A. SPIROMETRY

Measurement of FEV_1 is important to 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.

B. ELECTROCARDIOGRAM

ECG helps indicate the presence of late cor pulmonale.

C. 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.

D. CHEST RADIOGRAPHY (CXR)

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 for excluding other pulmonary diseases.

V. 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, 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 difficult treatment decisions, such as instituting oral or high dose inhaled corticosteroids. 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

a. 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.

b. 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 DoD/VHA Guideline on Smoking Cessation.

Clinicians should recommend smoking cessation at every visit; refer willing patients to establish smoking cessation program: Anthonison 1994, XU 1992, Camilli 1987, Fletcher 1977, LE=A, SR=I

2. Regular exercise

a. An informal program, with an emphasis on walking and upper body exercise, may help maintain physical functioning.
b. In more advanced disease, formal exercise training can be part of a comprehensive

rehabilitation program that, although expensive, may be beneficial.

3. Nutritional support

a. Undernutrition is associated with respiratory muscle weakness and increased mortality. The most-cost effective method for nutritional support in undernourished patients has not been established.

b. It is important in non-obese COPD patients to prevent weight loss. For any patient with poor appetite or eating-related dyspnea, frequent small meals may be more tolerable.

c. Weight reduction should be encouraged in obese patients.

C. PHARMACOTHERAPY

1. General considerations

a. Immunization with polyvalent pneumococcal vaccine and annual influenza vaccine is recommended by the Center for Disease Control, though evidence showing benefit with pneumococcal vaccination in COPD patients is controversial. Vaccination should be encouraged if the patient does not have contraindications.

Administer pneumococcal vaccine once at diagnosis if over age 65; otherwise at diagnosis and at age 65, provied at least 6 years have elapsed since the first dose was administered: CDC ACIP 1997, Fine 1994, Shapiro 1984, Shapiro 1991, Farr 1995, Sims 1988, Forrester 1987, Simberkoff 1986, LE=C. SR=IIa Administer influenza vaccine annually: CDC ACIP 1997, Govaert 1994, Nichol 1994, Gross 1988, Fedson 1993, Foster 1992, LE=C, SR=I

b. Metered - Dose Inhalers (MDI)

1) Because of a lower incidence of systemic adverse effects, inhaled bronchodilators are preferred to oral bronchodilators
2) Ensure proper education and technique in the use of MDI (Refer to Appendix 1)
3) Use spacers, as required, to enhance drug delivery
4) Emphasize the maximum doses of bronchodilator to avoid overuse
5) Educate the patient to use bronchodilators before exercise
6) Avoid complicated inhaler regimens as patient adherence to therapy declines
7) Consider other drug delivery systems(eg. dry powder inhalers) if patient cannot use MDI with spacer

c. Small Volume Nebulizer (SVN)

1) There is little evidence that nebulizer delivery offers improvement in COPD control over adequate MDI delivery for management of the stable COPD patient
2) Situations where an SVN is preferable include difficulty in managing a MDI (even after training with use of a spacer device) or other drug delivery systems, due to:
   i. impaired hand strength or dexterity

ii. visual impairment
iii. mental/cognitive problems
iv. inability to use an MDI during an acute exacerbation

3) SVN should be continued only if there is a clear clinical benefit

EVIDENCE

52% used MDI once daily or less rather than the required 3x daily: Rand 1995, LE=C, SR=I
50.6% adherence with nebulizers or intermittent positive pressure breathing: Turner 1995, LE=C, SR=I
Nebulizer dose of β-$_2$ agonist was twice that of MDI dose needed to produce maximum bronchodilation: Mestitz 1989, LE=B, SR=I
Dose of nebulized albuterol was 10x greater than MDI dose to produce same PEFR, FEV_1, or FVC: Jenkins 1987, LE=B, SR=I
Nebulized metaproteronol dose was 7x greater than that needed with MDI to achieve a similar outcome: Turner 1988, LE=B, SR=I

d. Drugs that can exacerbate COPD should be avoided; however, in some situations where the benefits of using the drug outweighs the risk (eg. beta-blockers post MI), the drug may be cautiously administered. Gottlieb 1998, LE=C, SR=IIa

2. Adrenergic agonists

a. These are available in MDI, dry powder inhalers, nebulizer and oral forms (Refer to Appendices 2 and 4). They can improve function and health-related quality of life.

b. Short-acting, selective β_2-agonists are preferred 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.

c. Short-acting β_2-agonists should be used "prn" for the majority of symptomatic patients with COPD. These agents may also be administered on a scheduled basis for those patients uncontrolled on ipratropium alone. The usual maximum dose is 12 puffs per day for short-acting agents such as albuterol, metaproterenol or terbutaline.

d. Symptoms may improve without substantial improvement in FEV_1 indicating that continuation of therapy does not depend on routine assessment with spirometry.

EVIDENCE

Metaproterenol 5 puffs improved the 12-minute walk compared to placebo. Spirometry was not improved: Berger 1988, E=C, SR=I
Dose related improvement in spirometry was seen with inhaled albuterol. 1mg as a single dose was most beneficial: Vathenen 1988, LE=B, SR=I
Average dose of inhaled albuterol for optimal improvement was 430mcg and for terbutaline, 1,160mcg. Upper end of range was 800 and 2500mcg respectively: Jaeschke 1993, LE=B, SR=I

e. The long-acting agent salmeterol, is approved for use in COPD. Most of the published studies using salmeterol for COPD compared salmeterol to placebo. In one study, salmeterol 42mcg twice daily produced greater sustained bronchodilation over a 12-hour period and increased the time to first COPD exacerbation when compared to ipratropium 36mcg four times daily. Other studies have shown that salmeterol can decrease the use of short-acting β_2-adrenergic agonists. Therefore, its use can be considered in patients who are using ipratropium and are requiring 12 or more puffs a day of a short-acting β_2-agonist. The short-acting agent should still be available for prn rescue use. Another potential role for salmeterol may be in patients with troublesome, nocturnal dyspnea. The role of salmeterol in the scheme of COPD therapy needs to be better defined. Salmeterol should only be continued in those patients who experience symptomatic benefit from its addition to their regimens. Because of the slow onset of effect, long-acting agents such as salmeterol, should not be used for acute shortness of breath.

EVIDENCE

Salmeterol compared to placebo resulted in small increase in FEV_1, decrease in dyspnea scores, and decrease use of prn albuterol over 16 weeks: Boyd 1997, LE=A, SR=I
Salmeterol compared to placebo improved AM PEFR, symptom scores, and decreased prn albuterol. There was no difference in FEV_1, FVC, FEV_1/FVC over 4 weeks: Ulrik 1995, LE=A, SR=IIa
Salmeterol compared to placebo improved FEV_1 at 1 and 6 hours and at 4 weeks. No difference in exercise tolerance: Grove 1996, LE=B, SR=I
Salmeterol 42mcg BID compared to ipratropium 36mcg QID produced greater sustained bronchodilation over 12 hours and increased the time to first COPD exacerbation: Mahler 1999, LE=A, SR=IIa

f. 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.

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 short-acting β_2-agonists have similar efficacy. Ipratropium has a slower onset of action, a longer duration of action, and minimal systemic absorption; thus, it may cause less severe systemic side effects than the β_2-agonists.

c. Use 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 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 also be used in patients who have daily symptoms.

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

e. Dosages higher than the manufacturers recommendations may be needed to produce

maximal improvement in pulmonary function. Improvement in level of physical functioning can be used to guide therapy.

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

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

EVIDENCE

Ipratropium increased baseline FEV_1 and FVC within 90days after initiation: Rennard 1996, LE=B, SR=IIa
Inhaled ipratropium 40mcg qid or metaproterenol 1.5mg qid were equally safe and effective over 90 day period: Tashkin 1986, LE=A, SR=I
No difference between albuterol 200mcg and ipratropium 40mcg; duration was l hour longer with ipratropium on day 85: Combivent 1994, LE=A, SR=I
Ipratropium produced greater and longer bronchodilation than albuterol: Braun 1989, LE=B, SR=IIa
Albuterol 400mcg qid versus ipratropium 80mcg qid had similar effects on distance walked and dyspnea: Blosser 1995, LE=B, SR=IIa
Sixteen patients responded only to albuterol, 17 only to ipratropium, 47 to albuterol + ipratropium, and 20 nonresponders, Nisar 1992: LE=C, SR=IIa
Between 6-14 puffs of ipratropium produced maximum increase in pulmonary function: Ikeda 1995, LE=B, SR=I
8-9 puffs of ipratropium is needed to give maximum benefit in pulmonary function and to give benefit at all with exercise: Ikeda 1996, LE=B, SR=I

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 an additive effect and lessen the risk of adverse effects from higher doses of a single agent.

b. A product combining albuterol 90mcg and ipratropium 18mcg in one metered dose inhaler is commercially available. This product should not be used as a first-line agent, but may be considered for patients who are well controlled on both individual agents in combination. Patients should be warned that this product is not for prn use and that they should use a short-acting β_2-agonist alone for break-through symptoms.

EVIDENCE

Ipratropium 80mcg plus albuterol 400mcg improved FEV_1 better than ipratropium 40mcg, ipratropium 80mcg or ipratropium 40mcg + albuterol 200mcg: Ikeda 1995, LE=C, SR=I
4 puffs ipratropium vs. 2 puffs ipratropium + 2 puffs metaproterenol produced no additional bronchodilation over 3hr period in stable COPD pts. However 2/12 pts. did benefit from the combination: LeDoux 1989, LE=B, SR=I
40mcg ipratropium plus 200mcg albuterol resulted in a greater increase in pulmonary function than either agent alone: Combivent 1994, LE=A, SR=I
Albuterol 800mcg + ipratropium 80mcg added at 90min produced the greatest improvement in FEV_1 when compared to other combinations: Easton 1986, LE=B, SR=IIa

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).

b. Several theophylline preparations are available (Refer to Appendix 5). 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 6).

e. Due to toxicity, the use of theophylline as monotherapy in COPD should be restricted to rare cases where patients cannot adequately administer inhalers.

f. Dosage should be carefully adjusted to achieve a peak plasma concentration between 8-15mcg/mL. This can be effective in increasing FEV_1 with less risk of adverse effects (Refer to Appendix 7). 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.

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.

EVIDENCE

2 months of theophylline at 14.8mcg/mL led to less dyspnea, an increase in pO2, a decrease in pCO2, and an increase in FVC and FEV_1: Murciano 1989, LE=A, SR=IIa
Theophylline at 9.5mcg/mL for 4 weeks improved pulmonary function and exercise performance: Newman 1994, LE=B, SR=IIa
Theophylline at 17mcg/mL maintained for 6 weeks improved PEFR, VC, symptoms, and decreased trapped gas volume. Patients prior bronchodilators or steroids were continued: McKay 1993, LE=B, SR=IIa
Withdrawal of theophylline (11mcg/mL) from inhaled beta-agonist and ipratropium led to a small decline in pulmonary function, an increase in symptoms, and less distance in the 6-minute walk test: Kirsten 1993, LE=A, SR=IIa
Theophylline at 12.2mcg/mL for 1 month when added to pre-study medications improved FVC and exercise: Fink 1994, LE=B, SR=IIa
Theophylline (9.1-16.4mcg/mL) improved gas exchange during rest, exercise, and sleep: Mulloy 1993, LE=B, SR=IIa
Theophylline 14.2mcg/mL improved FEV_1; SaO2 increased during rapid-eye movement sleep. There were fewer arousals; sleep

architecture was unaffected: Berry 1991, LE=B, SR=IIa
Twice daily theophylline (15mcg/mL) improved FEV_1 more than once daily dosing (11mcg/mL). SaO2 or sleep architecture was unaffected: Martin 1992, LE=B, SR=IIa
Theophylline at 9.2mcg/mL improved pulmonary function, reduced nocturnal wheezing, and improved nocturnal saturation. Sleep quality was unaffected: Man 1996, LE=B, SR=IIa
Theophylline 12.5mcg/mL for 2 weeks slightly improved FEV_1 and PEFR when added to inhaled salbutamol 200mcg and ipratropium 40mcg. Symptoms did not improve. Theophylline at 7.7mcg/mL did not add any additional benefit: Nishimura 1993, LE=B, SR=IIa
An additive effect on FEV_1 and PEFR was seen in ≈ 1/3 of pts. when theophylline (at 15mcg/mL) was combined with albuterol 400mcg qid and ipratropium 80mcg qid. More GI complaints with theophylline: Nishimura 1995, LE=B, SR=IIa
Combination of theophylline at 15.3mcg/ml and albuterol 2 puffs over 14 days improved pulmonary function more than either agent alone: Thomas 1992, LE=B, SR=IIa
Combination of theophylline at 12-18mcg/mL, albuterol 2 puffs, and ipratropium 2 puffs improved pulmonary function more than any of the agents alone over 6 hours: Karpel 1994, LE=A, SR=IIa

6. Corticosteroids

a. The use of corticosteroids remains controversial. Chronic oral corticosteroids are beneficial in less than about 20-25% of patients. The percent that benefit from inhaled steroids is not precisely defined.

b. If a patient appears to be a candidate for a trial of corticosteroids, a pulmonary consult should be considered.

c. A steroid response trial should be instituted only when the patient is stable, and is failing maximum bronchodilator therapy (Refer to Algorithm 1).

d. Either oral or high-dose inhaled steroids may be used for the trial. For example, prednisone 40mg/day for 2-3 weeks (or equivalent) or inhaled beclomethasone 1000-1500mcg/day for 6 weeks (or equivalent) is commonly used.

e. Improvement should be documented by spirometry. A response is defined as an increase of ≥20% in FEV_1 and a reduction of symptoms (eg. increased walking distance, decreased breathlessness).

f. If patient does not respond adequately to the trial, then discontinue the steroid.

g. If the patient responds to a trial of an oral steroid, begin to taper the steroid dosage and consider instituting an inhaled steroid as part of the taper. It is not known whether response to a short-term steroid trial predicts response to long-term inhaled steroids. The goal should be to use the lowest possible daily maintenance dose of corticosteroids. An individualized approach should be used to determine the minimum dosage needed to achieve the desired benefit.

- Since short-term (2-3 weeks) high-dose steroids do not produce serious toxicities, the ideal use is to administer the glucocorticoids in a short "burst" (up to 40 mg/day for 2-3 weeks). If oral steroid course improves airflow and symptoms, begin taper and consider institution of inhaled steroid during taper
- If maintenance oral steroids are required, taper dosage to the lowest effective dosage (eg. 7.5-10 mg/day) or to alternate-day dosing as quickly as possible
- Combination oral and inhaled steroids may be used as an oral steroid-sparing measure
- When determining the need for maintenance therapy, distinguish psychological benefit from true pulmonary benefit by measuring FEV_1 following 2-3 weeks of therapy. If no benefit is demonstrated, stop the steroid
- Repeatedly evaluate patients to determine if steroid therapy can be discontinued

h. Adverse effects of oral corticosteroids are numerous, including hypertension, hyperglycemia, weight gain, purpura, mental status changes, depression, glaucoma, cataracts, and adrenal suppression. Osteoporosis may occur within 6 months. Patients requiring long-term steroids should be evaluated for risk of osteoporosis and be treated preventively with calcium and vitamin D supplements, weight-bearing exercise, or hormone replacement therapy as appropriate. The risks of long-term steroid treatment should be discussed with the patient.

i. Patients who have received prolonged oral corticosteroid treatment should be given 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.

j. Transfer of a patient from systemic to inhaled steroids must be done slowly to avoid risk of adrenal insufficiency.

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

l. Maximum doses of inhaled corticosteroids vary among agents (Refer to Appendix 3).

EVIDENCE

Oral steroid meta-analysis: 30-80mg/d of oral prednisone or equivalent resulted in 20% improvement in FEV_1 in 10% of treated patients: Callahan 1991, LE=A, SR=I
Ten day course of alternate-day oral steroids was (64mg) as effective in improving FEV_1 as daily oral (8mg qid): Blair 1984, LE=B. SR=I
$\geq$ 7.5mg/d oral prednisolone slows decline of FEV_1 and improves survival in severe COPD: Postma 1985, LE=C, SR=IIa
A retrospective analysis showing, $\geq$ 10mg oral prednisolone decreases decline in FEV_1 in moderately severe COPD: Postma 1988,

LE=C, SR=IIa
Beclomethasone (1500-3000mcg./d) over 6 weeks produced a small improvement in FEV_1, FVC, and PEFR. 40mg/d of prednisolone added to inhaled beclomethasone did not further improve pulmonary function: Weir 1993, LE=A, SR=IIa
20% of patients had an improvement in FEV_1, taking prednisolone 40mg/d or inhaled beclomethasone 1500mcg/d, 17% responded to prednisone only and 5% responded to beclomethasone only over a 2 week period: Weir 1990a, LE=A, SR=IIa
Maximum benefit from oral prednisolone 40mg/d or inhaled beclomethasone 1500mcg/d can take more than 2 weeks. Effects from treatment may persist for longer than 2 weeks once therapy is withdrawn: Weir 1990b, LE=B, SR=I
20% of patients showed response to prednisolone 30mg/d x 2 weeks of whom over ¾ were considered as responders to inhaled bronchodilators: Nisar 1992, LE=C, SR=I
Similar response seen with a 2 week course of oral prednisolone 40mg/d and inhaled beclomethasone 1500mcg/d in patients without evidence of emphysema: Weir 1991, LE=A, SR=I
Addition of oral prednisolone 30mg/d produced further improvement in responders to inhaled beclomethasone 1500mcg/d: Wardman 1988, LE=C, SR=IIa
Meta-analysis: more than 800mcg of inhaled budesonide or beclomethasone was required for improvement in pulmonary function or symptoms: Van Schayck 1996, LE=A, SR=IIa
2 years of budesonide 800mcg/d plus either albuterol or ipratropium reduced the decline in FEV_1 and improved symptoms: Dompeling 1993, LE=C, SR=IIa
Budesonide 800mcg/d for 12 weeks decreased cough but did not improve any other measured symptom: Engel 1989, LE=B, SR=IIa
Budesonide 1600mcg/d for 2 years improved symptoms, and there were fewer drop-outs for pulmonary reasons compared to placebo: Renkema 1996, LE=A, SR=IIa
Budesonide 800mcg/d for 6 weeks improved FEV_1 and decreased prn beta-agonist use in patients demonstrating a response to bronchodilators: Weiner 1995, LE=B, SR=IIa
Meta-analysis: daily use of relatively high dose inhaled steroids for 2 years may slow the decline in FEV_1. The frequency of exacerbations did not decrease: Van Grunsven 1998, LE=B, SR=IIa
16% of patients treated with inhaled budesonide 750mcg qid for 4 weeks had a > 8.5% increase in FEV_1: Nishimura 1999, LE=A, SR=IIa
Fluticasone 500mcg/d x 6 months resulted in a decrease in severity of exacerbations, some improvement in PEFR, FEV_1, symptoms scores, and 6-min walking. Paggiaro 1998, LE=A, SR=IIa

D. MANAGEMENT OF ACUTE EXACERBATIONS

1. Signs and symptoms of acute exacerbation

Acute exacerbations can be defined as a recent deterioration in the patients' clinical and functional state, due to worsening of their COPD (ERS 1995 and BTS 1997). Typical

symptoms include:

- Worsening dyspnea
- Increased cough
- Increased sputum production
- Change in character or color of sputum
- Development of or increase in wheezing
- Loss of energy
- Increased respiratory rate
- Tachycardia
- Increased cyanosis
- Use of accessory muscles
- Peripheral edema
- Loss of alertness
- Worsening airflow obstruction
- Worsening arterial blood gases

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

A severe exacerbation is suggested by the loss of alertness plus at least two of the following: dyspnea at rest, respiratory rate >25/min, heart rate >110/min, increased cyanosis, and accessory use of muscles. 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, metaproterenol, or terbutaline are the bronchodilators of choice to treat COPD exacerbations. These agents can be beneficial by improving FEV_1 and dyspnea.

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.

EVIDENCE

Metaproterenol 3 puffs produced 18% increase in FEV_1: Karpel 1990, LE=B, SR=I
Albuterol 400mcg over 60 minutes produced 22% increase in FEV_1: Lloberes 1988, LE=B, SR=I

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 unable to use an 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.

EVIDENCE

Similar benefit from MDI or NEB metaproterenol on dyspnea or FEV_1 in ED patients: Turner 1988, LE=B, SR=IIa Similar effect of albuterol MDI or NEB on FEV_1 and dyspnea in hospitalized patients: Berry 1989, LE=B, SR=IIa Benefit from metaproterenol NEB 15mg > MDI 2 puffs on FVC in hospitalized patients: Maguire 1991, LE=B, SR=IIa

e. Inhaled ipratropium has been used to treat acute exacerbations of COPD. As a single agent, its effect on spirometry is equal to that of inhaled β_2-agonists. Because ipratropium has a slower onset of action, $beta_2$-agonists are usually preferred during acute exacerbations.

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.

EVIDENCE

Similar increase in FEV_1 following ipratropium or metaproterenol by MDI in ED and clinic patients: Karpel 1990, LE=B, SR=I Similar increase in FEV_1 following ipratropium, metaproterenol, or a combination of ipratropium/metaproterenol by nebulizer in ED patients: Rebuck 1987, LE=B, SR=I Ipratropium 4 puffs q 2-3 hours added to albuterol, steroids, and theophylline offered no additional improvement in FEV_1 over 24 hours in hospitalized patients: Patrick 1990, LE=B, SR=I Ipratropium 2-3 puffs following isoetharine shortened the duration of ED stay, but did not add to improvement in FEV_1: Shrestha 1991, LE=B, SR=I Addition of ipratropium to albuterol by nebulizer offered no additional improvement in PEFR when compared to albuterol alone in ED patients: O'Driscoll 1989, LE=B, SR=I

3. Corticosteroids

a. Corticosteroids have not shown consistent benefit in acute exacerbations. However, selected 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.

b. The dose, duration, and tapering of therapy for a course of oral steroids are not well established. Prednisone 0.6 - 0.8mg/kg/day for 7-14 days is often used in clinical practice. Upon completion of a steroid course and during a taper, the patient must be monitored for potential relapse. Often, a 1-2 week tapering schedule is used or one may use an individual patient's prior steroid history to determine a tapering schedule.

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 admisssion.

EVIDENCE

FEV_1 improved in hospitalized patients when methylprednisolone 0.5mg/kg IV q 6h was added to multidrug therapy: Albert 1980, LE=B, SR=IIa Early administration of single dose methylprednisolone 100mg IV did not improve FEV_1 or decrease hospitalizations in ED patients: Emerman 1989, LE=B, SR=IIa IV and oral steroids reduced relapse rate in ED patients with COPD exacerbation and a history of relapses: Murata 1990, LE=B, SR=IIa Oral prednisone improved FEV_1 and reduced treatment failure in an outpatient veteran population: Thompson 1996, LE=B, SR=IIa

4. Antibiotic Therapy

a. Antibiotic therapy is not indicated for all acute exacerbations of COPD.

b. If the exacerbation is associated with changes in sputum (quality, volume, or color), or increased cough or fever, treatment with antibiotics may be reasonable. 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.

d. Choice of antibiotic should consider local sensitivity patterns and patient allergies. Established antibiotics, such as amoxicillin, doxycycline or trimethoprim/sulfamethoxazole, are appropriate choices for the majority of cases.

e. 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, advanced COPD, or pneumonia.

EVIDENCE

Antibiotic therapy improved PEFR: Saint 1995, LE=B, SR=I Benefit from antibiotic therapy in prevention of further deterioration: Anthonisen 1987, LE=B, SR=I Antibiotics added to a short course of steroids did not improve PEFR or accelerate recovery in mild-moderate exacerabation in outpatients: Sachs 1995, LE=B, SR=I

5. Theophylline

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

b. If the patient is already on theophylline, adjust the dosage, as necessary, to achieve a serum concentration of 8-15mcg/mL. Keep in mind that certain factors such as antibiotics or fever can alter theophylline concentrations. (Refer to Appendix 6)

c. In general, if the patient is not on theophylline, there is no need to start it in the setting of an acute exacerbation.

EVIDENCE

Aminophylline did not add any benefit to standard multidrug therapy in hospitalized patients: Rice 1978, LE=B, SR=IIb Aminophylline did not add any measurable or symptomatic benefit, though there was a trend toward decreased admission rates in ED patients: Wrenn 1991, LE=B, SR=IIb

E. OXYGEN THERAPY

Long-term oxygen therapy can reverse secondary polycythemia, increase body weight, alleviate right heart failure due to cor pulmonale, augment cardiac function, increase exercise performance, and increase survival for patients with resting hypoxemia. Refer to VHA guidelines on long term oxygen therapy, module A5 p. 70 or the Home Use of Supplemental Oxygen Program: A Source Book; September 1998 National Center of Cost Containment.

References

Albert RK, Martin TR, Lewis S. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. Ann Intern Med 1980;92:753-758.

American College of Rheumatology Task Force on Osteoporosis Guidelines. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis and Rheumatism 1996;11:1791-1801.

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.

Anthonisen NR, Manfreda J, Warren CPW, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.

Anthonisen NR, Connett JE, Kiley JP, et al. Lung Health Study Research Group: Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: The Lung Health Study. JAMA 1994;272:1497-1505.

Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. Am J Resp Crit Care Med 1998;157:S1-S53.

Berger R, Smith D. Effect of metaproterenol and exercise performance in patients with stable fixed airway obstruction. Am Rev Respir Dis 1988;138:624-629.

Berry RB, Shinto RA, Wong FH, et al. Nebulizer vs spacer for bronchodilator delivery in patients hospitalized for acute exacerbations of COPD. Chest 1989;96:1241-1246.

Berry RB, Desa MM, Branum JP, et al. Effect of theophylline on sleep and sleep-disordered breathing in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1991;143:245-250.

Blair GP, Light RW. Treatment of chronic obstructive pulmonary disease with corticosteroids: comparison of daily vs alternate-day therapy. Chest 1984;86:524-528.

Blosser SA, Maxwell SL, Reeves-Hoche MK, et al. Is an anticholinergic agent superior to a beta2-agonist in improving dyspnea and exercise limitation in COPD. Chest 1989;96:1241-1246.

Bowton DL, Goldsmith WM, Haponik EF. Substitution of metered dose inhalers for hand-held nebulizers: Success and cost-savings in a large, acute-care hospital. Chest 1992;101:305-308.

Boyd G, Morice AH, Pounsford JC, et al. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). Eur Respir J 1997;10:815-821.

Braun SR, Wayland NM, Copeland C, et al. A comparison of the effect of ipratropium and albuterol in the treatment of chronic obstructive airway disease. Arch Intern Med 1989;149:544-547.

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

Callahan CM, Dittus RS, Katz BP. Oral corticosteroid therapy for patients with stable chronic obstructive pulmonary disease. Ann Intern Med 1991;114: 216-223.

Camilli AB, Burrows B, Knudson RJ, et al. Longitudinal changes in forced expiratory volume in one second in adults: effects of smoking and smoking cessation. Am Rev Respir Dis 1987;135:794-799.

Combivent Inhalation Aerosol Study Group in Chronic Obstructive Pulmonary Disease. A combination of ipratropium and albuterol is more effective than either agent alone: An 85 day multicenter trial. Chest 1994;105:1411-1419.

Department of Veterans Affairs Clinical Practice Guidelines for the Management of Persons with Chronic Obstructive Pulmonary Disease or Asthma. Version 1.0 1997.

Dompeling E, van Schayck CP, van Grunsvan PM, et al. Slowing the deterioration of asthma and chronic obstructive pulmonary disease observed during bronchodilator therapy by adding inhaled corticosteroids: A 4-year prospective study. Ann Intern Med 1993;118:770-778.

Easton PA, Jadne C, Dhingra S, et al. A comparison of the bronchodilating effects of a beta-adrenergic agent (albuterol) and an anticholinergic agent (Ipratropium bromide) given by aerosol alone or in sequence.
N Eng J Med 1986;315:735-739.

Emerman CL, Connors AF, Lukens TW, et al. A randomized, controlled trial of methylprednisolone in the emergency treatment of acute exacerbations of COPD. Chest 1989;95:563-567.

Engel T, Heinig JH, Madsen O, et al. A trial of inhaled budesonide on airway responsiveness in smokers with chronic bronchitis. Eur Respir J 1989;2:935-939.

Farr BM, Johnston BL, Cobb DK, et al. Preventing pneumococcal bacteremia in patients at risk: results of a matched case-control study. Arch Intern Med 1995; 155:2336-2340.

Fedson DS, Wajda A, Nicol JP, et al. Clinical effectiveness of influenza vaccination in Manitoba. JAMA 1993;270:1956-1961.

Fine MI, Smith MA, Carson CA, et al. Efficacy of pneumococcal vaccination in adults: a meta-analysis of randomized controlled trials. Arch Intern Med 1994;154:2666-2677.

Fink G, Kaye C, Sulkes J, et al. Effect of theophylline in exercise performance in patients with severe chronic obstructive pulmonary disease. Thorax 1994;49:332-334.

Fletcher CM, Peto R. the natural history of chronic airflow obstruction. BMJ 1977;1:1645-1648.

Forrester HL, Jahnigen DW, LaForce FM. Inefficacy of pneumococcal vaccine in a high-risk population. Am J Med 1987;83:425-430.

Foster DA, Talsma A, Furumoto-Dawson A, et al. Influenza vaccine effectiveness in preventing hospitaliization for pneumonia in the elderly. Am J Epidemiol 1992;136:296-307.

Gottleib SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med 1998;339:489-497.

Govaert T, Thijs CTMCN, Masurel N, et al. The efficacy of influenza vaccinein elderly individuals: a randomized double-blind placebo-controlled trial. JAMA 1994;272:1661-1665.

Gross NJ. Ipratropium bromide. N Eng J Med 1988;319:486-494.

Gross PA, Quinnan GV, Rodstein M, et al. Association of influenza immunization with reduction in mortality in an elderly population: a prospective study. Arch Intern Med 1988;148:562-565.

Grossman RI. Guidelines for the treatment of acute exacerbations of chronic bronchitis. Chest 1997;112:310S-313S.

Grove A, Lipworth BJ, Reid P, et al. Effects of regular salmeterol on lung function and exercise capacity in patients with chronic obstructive airways disease. Thorax 1996;51:689-693.

Hendeles L, Jenkins J, Temple R. Revised FDA labeling guideline for theophylline oral dosage forms. Pharmacotherapy 1995;15(4):409-427.

Hudson LD, Monti CM. Rationale and use of corticosteroids in chronic obstructive pulmonary disease. Med Clin N Amer 1990;74:661-689.

Ikeda A, Nishimura K, Koyama, H, et al. Bronchodilating effects of combined ipratropium bromide and salbutamol for stable COPD. Chest 1995; 107:401-405.

Jaeschke R, Guuyatt GH, Cook D, et al. The effect of increasing doses of beta-agonists on airflow in patients with chronic airflow obstruction. Respiratory Med 1993; 87:433-438.

Jenkins SC, Heaton W, Fulton TJ, et al. Comparison of domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. Chest 1987;91:806-807.

Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. Am J Respir Crit Care Med 1997;155:1283-1289.

Karpel JP, Kotch A, Zinny M, et al. A comparison of inhaled ipratropium, oral theophylline plus inhaled β_2 -agonist, and the combination of all three in patients with COPD. Chest 1994;105:1089-1094.

Karpel JP, Pesin J, Greenberg D, et al. A comparison of the effects of ipratropium bromide and metaproterenol sulfate in acute exacerbations of COPD. Chest 1990;98: 835-839.

Kelly HW. Comparison of inhaled corticosteroids. Annals of Pharmacother 1998;32:220-232.

Kirsten D, Wegner RE, Jorres RA, et al. Effects of theophylline withdrawal in severe chronic obstructive pulmonary disease. Chest 1993;104:1101-1107.

Kottke TE, Battista RN, DeFriese GH. Attributes of successful smoking cessation interventions in medical practice: A meta analysis of 39 controlled trials. JAMA 1988;259:2882-2889.

Lacasse Y, Wong E, Guyatt GH, et al. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. Lancet 1996;348:1115-19.

Le Doux EJ, Morris JF, Temple WP, et al. Standard and double dose ipratropium bromide and combined ipratropium bromide and inhaled metaproterenol in COPD. Chest 1989;95:1013-1016.

Lloberes P, Ramix L, Montserrat JM, et al. Effects of three different bronchodilators during an exacerbation of chronic obstructive pulmonary disease. Eur Respir J 1988;1:536-539.

Maguire GP, Newman T, DeLorenzo LJ, et al. Comparison of a hand-held nebulizer with a metered dose inhaler-spacer combination in acute obstructive pulmonary disease. Chest 1991;100:1300-1305.

Mahler DA, Donohue JF, Barbee RA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. Chest 1999;115:957-965.

Man GCW, Chapman KR, Ali SH, et al. Sleep quality and nocturnal respiratory function with once-daily theophylline (Uniphyl) and inhaled salbutamol in patients with COPD. Chest 1996;110:648-653.

Martin RJ, Pak J. Overnight theophylline concentration and effects on sleep and lung function in chronic obstructive pulmonary disease. Am Rev Respir Dis 1992;145:540-544.

McKay SE, Howie CA, Thomson AH, et al. Value of theophylline treatment in patients handicapped by chronic obstructive lung disease. Thorax 1993;48:227-232.

Mestitz H, Copland JM, McDonald CF. Comparison of outpatient nebulized vs metered dose inhaler terbutaline in chronic airflow obstruction. Chest 1989; 96:1237-1240.

Moayyedi P, Congleton J, Page RL, Pearson SB, Muers MF. Comparison of nebulised salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. Thorax 1995;50:834-837.

Mulloy E, McNicholas WT. Theophylline improves gas exchange during rest, exercise, and sleep in chronic obstructive pulmonary disease. Am Rev Respir Dis 1993;148:1030-1036.

Murata GH, Gorby MS, Chick TW, et al. Intravenous and oral corticosteroids for the prevention of relapse after treatment of decompensation COPD. Effects on patients with a history of multiple relapses. Chest 1990;98:845-848.

Murciano D, Auclair M-H, Patiente R, et al. A randomized controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. N Engl J Med 1989;320:1521-1525.

Nelson HS. β-adrenergic bronchodilators. N Eng J Med 1995;333:499-506.

Newman D, Ramir J, Speedy L, et al. Physiologic and neurophysiological effects of theophylline in chronic obstructive pulmonary disease. Israeli J Med Sci 1994;30:811-816.

Nichol KL, Margolis KL, Wuorenma I, et al. The efficacy and cost effectiveness of vaccination against influenza

among elderly persons living in the community. N Engl J Med 1994;331:778-784.

Nisar M, Earis JE, Pearson MG, et al. Acute bronchodilator trials in chronic obstructive pulmonary disease. Am Rev Respir Dis 1992; 146:555-559.

Nishimura K, Koyama H, Ikeda A, et al. Is oral theophylline effective in combination with both inhaled anticholinergic agent and inhaled beta2-agonist in the treatment of stable COPD. Chest 1993;104:179-184.

Nishimura K, Koyama H, Ikeda A, et al. The additive effect of theophylline on a high-dose combination of inhaled salbutamol and ipratropium bromide in stable COPD. Chest 1995;107:718-723.

Nishimura K, Koyama H, Ikeda A, et al. The effect of high-dose inhaled beclomethasone in patients with stable COPD. Chest 1999;115:31-37.

Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 1980; 93:391-398.

O'Donohue WJ. A National Association for Medical Direction of Respiratory Care (NAMDRC) Consensus Group. Guidelines for the use of nebulizers in the home and at domiciliary sites: Report of a consensus conference. Chest 1996;109:814-820.

O'Driscoll BR, Taylor RJ, Horseley MG, et al. Nebulized salbutamol with and without ipratropium bromide in acute airflow obstruction. Lancet 1989;2:1418-1420.

Paggiaro PL, Dahle R, Bakran I, Frith L, et al on behalf of the international COPD group. Multicenter randomized, placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. Lancet 1998;351:773-780.

Patrick DM, Dales RE, Stark RM, et al. Severe exacerbation of COPD and asthma. Incremental benefit of adding ipratropium to usual therapy. Chest 1990;98:295-297.

Postma DS, Steenhuis EJ, Van der Weele T, et al. Severe chronic airflow obstruction: can corticosteroids slow down progression? Eur J Respir Dis 1985;67:56-64.

Postma DS, Peters I, Steenhuis EJ, et al. Moderately severe chronic airflow obstruction: Can corticosteroids slow down progression? Eur Respir J 1988;1:22-26.

Ramsdell J. Use of theophylline in the treatment of COPD. Chest 1995;107(Suppl 5):206S-209S.

Rand CS, Nides M, Cowles MK, et al and the Lung Health Research Group: Long-term metered-dose inhaler adherence in a clinical trial. Am J Respir Crit Care Med 1995;152:580-588.

Rebuck AS, Chapman KR, Aboud R, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. Am J Med 1987;82:59-64.

Renkema TEJ, Schouten JP, Koeter GH, Postma DS. Effects of long-term treatment with corticosteroids in COPD. Chest 1996;109:156-1162.

Rennard SI. Combination bronchodilator therapy in COPD. Chest 1995;107(Suppl 5):171S-175S.

Rennard SI, Serby CW, Ghafouri M, et al. Extended therapy with ipratropium is associated with improved function in patients with COPD. Chest 1996;110:62-70.

Rice KL, Learterman JW, Duane PG, et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. A controlled trial. Ann Intern Med 1987;107:305-309.

Sachs APE, Koeter GH, Groenier KH, et al. Changes in symptoms, peak expiratory flow, and sputum flora during treatments with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease general practice. Thorax 1995;50:758-763.

Saint S, Bent S, Vittinghoff E, et al. Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. JAMA 1995;272:957-963.

Shannon M, Lovejoy FH. The influence of age vs. peak serum concentration of life threatening events after chronic theophylline intoxication. Arch Intern Med 1990;150:2045-2048.

Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med 1991;325:1453-1460.

Shapiro ED, Clemens JE. A controlled evaluation of the protective efficacy of pneumococcal vaccine for patients at high risk of serious pnuemococcal infections. Ann Intern Med 1984;101:325-330.

Shrestha M, O'Brien T, Haddox R, et al. Decreased duration of emergency department treatment of chronic obstructive pulmonary disease exacerbations with the addition of ipratropium bromide to beta-agonist therapy. Ann Emerg Med 1991;20:1206-1209.

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.

Simberkoff MS, Cross AP, Al-Ibrahim M. Efficacy of pneumococcal vaccine in high-risk patients. N Engl J Med 1986;315:1318-1327.

Sims RV, Steinmann WC, McConville JH, et al. The clinical effectiveness of pneumococcal vaccine in the elderly. Ann Intern Med 1988;108:653-657.

Tang JL, Law M, Wald N. How effective is nicotine replacement therapy in helping people to stop smoking? Br Med J 1994;308:21-26.

Tashkin DP, Ashutesh K, Bleeker ER, et al. Comparison of the anticholinergic bronchodilator ipratropium bromide with metaproterenol in chronic obstructive pulmonary disease: A 90 day multicenter study. Am J Med 1986;81(Suppl 5A):81-83.

Thomas P, Pugsey JA, Stewart JH. Theophylline and salbutamol improve pulmonary function in patients with irreversible chronic obstructive pulmonary disease. Chest 1992;101:160-165.

Thompson WH, Nielson CP, Carvalho P, et al. Controlled trial of oral prednisone in outpatients with acute

COPD exacerbation. Am J Respir Crit Care Med 1996;154:407-412.

Turner J, Wright E, Mendella L, Anthonisen N and the IPPG Study Group. Predictors of patient adherence to long-term home nebulizer therapy for COPD. Chest 1995;108:394-400.

Turner JR, Corkery KJ, Eckman D, et al. Equivalence of continuous flow nebulizer and metered dose inhaler with reservoir bag for treatment of acute airflow obstruction. Chest 1988;93:476-481.

Ulrik CS. Efficacy of inhaled salmeterol in the management of smokers with chronic obstructive pulmonary disease: A single-center, randomized, double-blind, placebo-controlled crossover study. Thorax 1995;50:750-754.

Van Grunsven PM, van Schayck CP, Derenne JP, et al. Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis. Thorax 1999;54:7-14.

Van Schayck CP, Van Grunsven PM, Dekhuijzen PNR. Do patients with COPD benefit from treatment with inhaled corticosteroids? Eur Respir J 1996;9:1969-1972.

Vathenen AS, Britton JR, Ebden P, et al. High-dose inhaled albuterol in severe chronic airflow limitation. Am Rev Respir Dis 1988;138:850-855.

VHA/DoD Clinical practice guideline to promote tobacco use cessation in the primary care setting (May 1999). "Tobacco Use Cessation" V101(93)P-1633. Veterens Health Administration/Department of Defense.

Wardman AG, Simpson FG, Knox AJ, et al. The use of high dose inhaled beclomethason dipropionate as a means of assessing steroid responsiveness in obstructive airways disease. Br J Dis Chest 1988;82:168-171.

Weiner P, Weiner M, Azgad Y, et al. Inhaled budesonide therapy for patients with stable COPD. Chest 1995;108:1568-1571.

Weir DC, Gove RI, Robertson AS, et al. Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone dipropionate. Thorax 1990a:45:112-117.

Weir DC, Robertson AS, Gove RI, et al. Time course of response to oral and inhaled corticosteroids in non-asthmatic chronic airflow obstruction. Thorax 1990b:45:118-121.

Weir DC, Gove RI, Robertson AS, et al. Response to corticosteroids in chronic airflow obstruction: relationship to emphysema and airways collapse. Eur Respir J 1991;5:1185-1190.

Weir DC, Burge PS. Effects of high dose inhaled beclomethasone dipropionate, 750mcg and 1500mcg twice daily, and 40mg per day oral prednisolone on lung function, symptoms and bronchial hyperrresponsiveness in patients with non-asthmatic chronic airflow obstruction. Thorax 1993;48:309-316.

Wrenn K, Slovis CM, Murphy F, et al. Aminophylline therapy for acute bronchospastic disease in the emergency room. Ann Intern Med 1991;115:241-247.

Xu X, Dockery DW, Ware HJ, et al. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. Am Rev Respir Dis 1992;146:1345-1348.

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

Only 10 - 15 % of the spray reaches the lungs

Only a minority of users perform correct technique

Instructions:

- Remove the cap and shake the inhaler thoroughly
- Breathe out slowly
- 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

If technique is inadequate use a spacer device

Emphasize and monitor compliance with the use of MDIs

[a] Adapted from Newman SP, Clarke SW. The proper use of metered-dose inhalers. Chest 1984;86:342-343.

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

DRUG	MDI DOSE	USUAL MDI PUFFS[c]	MAXIMUM DOSES	USUAL DOSES OF NEBULIZER SOLUTIONS[e]	PRECAUTIONS IN DRUG USE
Adrenergic Agents					When using β_2-agonists: •Use spacers to enhance delivery and reduce systemic effects •Avoid overuse: check # of MDIs used per month against # of puffs per MDI (200 - 300+ depending on manufacturer) •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	0.09 mg	1-2 q 4-6 h	12 puffs/day[d]	0.5 mL (2.5 mg)[f] or 3.0 mL (2.5mg)[f]	
Bitolterol	0.37 mg	2-3 q 4-8 h	12 puffs/day	0.25-1 mL (0.5-2 mg)	
Metaproterenol	0.65 mg	2-3 q 3-4 h	12 puffs/day	0.2-0.3 mL (10-15 mg)[f] or 2-5 mL (10 mg)[f]	
Pirbuterol	0.20 mg	1-2 q 4-6 h	12 puffs/day	or 2-5 mL (15 mg)[f]	
Salmeterol	0.02 mg	2 q 12h	4puffs/day	—	
Terbutaline	0.20 mg	2 q 4-6 h		—	
Anticholinergic Agents					•Caution patient that onset of effect is relatively slow: additional doses should not be taken for acute symptomatic relief •Monitor for side effects (e.g. tachycardia, dry mouth, glaucoma, bladder neck obstruction or prostatism)
Ipratropium	0.018 mg	2 - 3 q 6 h	12 puffs/day[d]	2.5 mL (0.5 mg)	
Combination Products					• Use activator supplied by manufacturer only • Same warnings as above for ipratropium • May be used in patients well-controlled on each individual agent
Albuterol + ipratropium	0.09mg/ 0.018mg	2-3 q 6 h	12 puffs/day	—	

[a] Adapted from ATS statement[1]
[b] Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc.,1996.
[c] These are usual recommended **maintenance** doses, although they may be modified in particular clinical circumstances
[d] Maximum doses per manufacturer's recommendations, although higher doses have been used clinically
[e] Unit dose is the standard dose recommended for adults. Usually available in 0.25-2.5 mL, and percentage delivered to lungs depends on both nebulizer and breathing technique used
[f] Dosage depends on brand

Appendix 3. Dosages of Inhaled Steroids in COPD[a,b]

Inhaled Steroid	Usual dosing interval	# of puffs/day for low-medium dose	# of puffs/day for high-dose use[c]
Beclomethasone • 42 mcg • 84mcg	 q 6-8h or q 12h q 12 h	 4-20 2-10	 > 20 > 10
Budesonide 200mcg	q 12h	1-3	> 3
Fluticasone • 44 mcg • 110 mcg • 220 mcg	 q 12h	 2-6 2-6 -	 - > 6 > 3
Flunisolide 250 mcg	q 12h	2-8	> 8
Triamcinolone 100 mcg	q 6-8h or q 12h	4-20	> 20

[a]Adapted from VHA Clinical Practice Guideline for COPD

[b]Not yet approved by the FDA for COPD

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

Appendix 4. Dosages of Oral Medications in COPD[a,b]

DRUG	ORAL DOSE	PRECAUTIONS
Albuterol	IR: 2 - 4 mg tid - qid, max 8 mg qid SR: 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 3 - 4 times daily	
Terbutaline[c]	5 mg tid	
Prednisone	up to 40 mg qd	• Adverse effects include: hypertension, hyperglycemia, weight gain, purpura, mental status changes, depression, glaucoma, cataracts, adrenal suppression, osteoporosis (within 6 months)

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

[b] IR = immediate release; SR = sustained release

[c]Terbutaline is also available for subcutaneous administration: 0.25 - 0.5 mg (do not exceed 0.5 mg in 4 h)

Appendix 5. Sustained-Release Theophylline Preparations with Complete Absorption[a-b]

FORMULATION	DOSING INTERVAL	COMMENTS
Theophylline (various manufacturers) Generic preparations available in liquid, capsule, and tablet forms	1 - 3 times/day	• Complete absorption occurs in the presence or absence of food • Scored tablets can be split without affecting absorption characteristics • AB rated products are recommended[c] • Immediate release formulations should be avoided due to short half-life, especially in smokers
Slo-bid Gyrocap® Capsules 100, 125, 200, 300 mg	2 - 3 times/day	• Can be opened and sprinkled on a spoonful of soft food for those who can not swallow the capsule • Complete absorption occurs in the presence or absence of food • Contents must be swallowed without chewing
Uni-Dur® Tablets 400, 600 mg Uniphyl® Tablets 400 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 • Uni-Dur® similar to Theo-Dur® tablets but more slowly absorbed • Near complete absorption occurs in the presence or absence of food (Uni-Dur®) • Incomplete absorption occurs when taken after an overnight fast (Uniphyl® and Theo-24®) • More complete absorption occurs when taken after food or in the evening (Uniphyl® and Theo-24®) • pH-dependent dissolution causes more rapid and complete absorption when taken after food or in the evening

[a] Bronchodilators. In: Hebel SK, ed. Facts and Comparisons, St. Louis: Facts and Comparisons Inc.,p178-179a.
[b] 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 .
[c] AB rated = as products meeting necessary bioequivalence requirements from Approved Drug Products . Rockville, MD: U.S. Department of Health and Human Services; 16th ed., 1996.

Appendix 6. Factors That Can Affect Theophylline Levels[a]

Drugs or factors decreasing theophylline clearance	Drugs or factors increasing theophylline clearance

allopurinol (≥ 600 mg/day), cimetidine, ciprofloxacin, clarithromycin, disulfiram, enoxacin, erythromycin, estrogen, fluvoxamine, interferon, methotrexate (low dose), mexiletine, pentoxifylline, propafenone, propranolol, tacrine, ticlopidine, troleandomycin, verapamil, zileuton, 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); carbamazepine; isoniazid; moricizine; phenobarbital; phenytoin; rifampin

[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

Appendix 7. Dosing and Adjustment Guidelines for Theophylline in Adults (as Anhydrous Theophylline)

Dosing guidelines[a]

To establish the daily dose requirement, it is generally recommended to begin treatment with a prompt release formulation. Once the proper dosage is determined, the patient may be switched to a sustained-release formulation.

A. Adults (16-60 years) Without Risk Factors for Impaired Clearance

Titration Step	Adults
1. Starting Dosage	300 mg/day divided q 6-8 hours
2. After 3 days, if tolerated, increase dose to:	400 mg/day divided q 6-8 hours
3. After 3 more days, if tolerated, increase dose to:	600 mg/day divided q 6-8 hours

B. 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
- Maintenance doses should not exceed 400 mg/day, unless patients are symptomatic and their peak (measured one hour post dose) steady state serum theophylline concentration is < 10mcg/mL

[a] Adapted from Hendeles L, Jenkins J, Temple R. Revised FDA labeling guideline for theophylline oral dosage forms. Pharmacotherapy 1995;15(4):409-427.

Final Dosage Adjustment Guided by Serum Theophylline Concentration[a,b]

PEAK SERUM CONCENTRATION	DOSAGE ADJUSTMENT
< 8 mcg/mL	• If symptoms are not controlled and current dosage is tolerated, increase daily dose about 25% • Recheck serum concentration after 3 days
8-15 mcg/mL	• If symptoms are controlled and current dosage is tolerated, maintain dose and recheck serum concentration at 6-12 month intervals
15.1-19mcg /mL	• Consider 10% decrease in daily dose to provide greater margin of safety even if current dosage is tolerated
19.9-25 mcg/mL	• Withhold next dose, then resume treatment with next lower dose increment
> 25 mcg/mL	• Withhold next 2 doses, then resume treatment with initial dose or lower dose

[a] Adapted from Weinberger M, Hendeles L. Drug Therapy: Theophylline in asthma. N Eng J Med 1996;334:1380-1388.

[b] **The guidelines listed use doses that are lower than in previous guidelines to account for the most recent assessment of population dose requirements and to minimize the risk of even minor adverse events.** With the use of these guidelines, one to two measurements of serum theophylline are usually sufficient to determine the dose requirement, with periodic checks thereafter unless clinical indications suggest the need for more frequent assessment.

Appendix 8. Selected Costs for COPD Drug Therapy (as of 6/99)

For current prices, check Drug & Pharmaceutical Product Management Bulletin Board # 708-531-7947

DRUG	USUAL DOSE [a]	PUFFS PER MDI	FEDERAL SUPPLY SCHEDULE (FSS) COST/INHALER	FEDERAL SUPPLY SCHEDULE (FSS) COST/MONTH
Inhaled Adrenergic Agents				
Albuterol	1-2 puffs q 4-6 h	200	$ 1.75	2 inhalers/month = $3.50
Bitolterol	2 puffs q 4-8 h	300	$ 6.97	1 inhaler/month = $ 6.97
Metaproterenol	1-2 puffs q 3-4 h	200	$ 11.67	2 inhalers/month = $23.34
Pirbuterol	1-2 puffs q 4-6 h	300	$ 16.13	1 inhaler/month = $16.13
Salmeterol	2 puffs q 12 h	120	$ 32.52	1 inhaler/month = $32.52
Terbutaline	2 puffs q 4-6 h	300	$ 11.16	1 inhaler/month = $11.16
Anticholinergic Agent				
Ipratropium	2-3 puffs q 6 h	200	$ 16.93	2 inhalers/month = $33.86
Combination Product				
Albuterol/ipratropium	2 puffs q 6 h	200	$ 20.61	2 inhalers/month = $41.22
Inhaled Corticosteroids				
Beclomethasone 42mcg	2-4 puffs q 6 h	200	$ 3.49	2 inhalers/month = $6.98
Budesonide	1-2 puffs q 12 h	200	$ 67.76	1 inhaler/month = $67.76
Flunisolide	2-4 puffs q 12 h	100	$ 2.80	2 inhalers/month = $ 5.60
Fluticasone 220 mcg[b]	2-4 puffs q 12 h	120	$ 46.20	2 inhalers/month = $92.40
Triamcinolone	2-4 puffs q 6 h	240	$ 9.65	2 inhalers/month = $19.30

[a] Usual doses; does not reflect equivalent doses

DRUG	USUAL DOSE [a]	FEDERAL SUPPLY SCHEDULE (FSS) COST/MONTH
Oral Adrenergic Agents		
Albuterol	IR: 2-4 mg tid-qid	2 mg tablets: $1.04 - 1.39
		4 mg tablets: $ 1.39 - 1.86
	SR: 4 mg q 12 h	$ 20.88
Metaproterenol	10 mg tid - qid	$ 14.69 - 19.58
Terbutaline	5 mg tid	$ 22.00
Oral Corticosteroid		
Prednisone	up to 40 mg qd	5 mg tablets: $ 1.48
Theophylline Preparations		
Slo-bid®	300 mg bid-tid	$ 6.01-9.02
Theo-Dur®	300 mg qd-tid	$ 3.50-10.49
Uni-Dur®	400 mg qd	$ 17.34
Uniphyl®	400 mg qd	$ 25.50[b]

[a] Usual doses; does not reflect equivalent doses
[b] Average wholesale price