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## Medical Management of Chronic Obstructive Pulmonary Disease: Focus on Federal Healthcare

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## Supplement

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## MEDICAL MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: FOCUS ON FEDERAL HEALTHCARE

This supplement to the *Journal of Managed Care Medicine* is based on presentations and discussions at a clinical consensus meeting that took place Oct. 15, 2005, and sponsored by the National Association of Managed Care Physicians Inc. and Hospicom Inc.

### Target Audience

This activity is intended for pharmacy and therapeutics committee members, medical directors, infectious disease physicians, pulmonologists, internists, and primary care physicians who care for patients with chronic obstructive pulmonary disease.

### Needs Assessment

Although chronic obstructive pulmonary disease (COPD) affects only nine percent of patients in the Veterans Affairs (VA) system, the average annual cost per patient is higher than that of any other illness.

Therapy has evolved over the past few decades, with long-acting bronchodilators now considered to be the mainstay of therapy, particularly in moderate-to-severe cases.\* Physicians employed in the VA system frequently are required to prescribe treatments for COPD according to guidelines that do not always reflect current thinking in the wider medical community. The guidelines often sacrifice long-term cost savings for short-term economic benefits.

This supplement, developed by experts in COPD management, outlines the evidence supporting the need for revisions to the guidelines that incorporate newer, more effective agents.

### Learning Objectives

Upon completing this activity, the reader will be able to:

- Understand the historical perspective on the approach to managing COPD
- Describe the role of cholinergic activity in COPD
- Understand the pharmacology of long-acting bronchodilators
- Understand the impact of acute exacerbations on COPD
- Discuss the pharmacoeconomic burden of COPD

\*Dorinsky, PM, C. Reisner, et al. The combination of ipratropium and albuterol optimizes pulmonary function reversibility testing in patients with COPD. *Chest* 1999;115(4): 966-971.

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This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for

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The release date of this activity is May 1, 2006. This activity is valid through May 1, 2007.

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# Introduction: Chronic Obstructive Pulmonary Disease

Thomas J. Ferro, MD, and  
Douglas B. Schwartz, MD

Among the most commonly treated respiratory diseases, chronic obstructive pulmonary disease (COPD) accounts for the largest slice of the healthcare budget in the Veterans Health Administration (VHA). COPD is the most expensive chronic condition with regard to average inpatient medical/surgical costs. Over the years, professional societies and national organizations

such as the American Thoracic Society have produced guidelines for the management of COPD. The latest among these is the Global Initiative for Obstructive Lung Disease (GOLD), which frequently is revised to take into account new additions to the pharmacological armamentarium.

The VHA also is revising its practice guidelines to reflect the latest benefit and cost data. National and international guidelines generally recommend the initial use of short-acting therapies because they carry with them lower acquisition costs than do long-acting therapies, such as long-acting  $\beta_2$  agonists and the long-acting anticholinergic agent, tiotropium. However, there is mounting evidence that long-acting agents, alone or in combination, can improve symptoms and outcomes, and reduce the need for

expensive high-morbidity care such as hospitalizations.

The articles in this supplement review the existing guidelines (both Veterans Affairs and non-VA), the pharmacology and efficacy of available medications, the impact of COPD on the VHA, and the rationale for existing guidelines. After reviewing the available data, our panel of experts offers its own consensus statement for the reader's consideration. **JMCM**

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## Disclosure of Faculty Relationships and Discussion of Off-Label Uses

The faculty provided the following information regarding significant commercial relationships and/or discussions of investigational or non-FDA approved (off-label) uses of drugs:

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# A Historical Perspective on Chronic Obstructive Pulmonary Disease—the Evolution of Management

Donald P. Tashkin, MD

## Summary

During the last century, the array of pharmacological therapies for chronic obstructive pulmonary disease (COPD) has expanded considerably. Although each new addition to the armamentarium of available options promises to improve management of the disease, it also exponentially increases the complexity of designing a safe, effective regimen for individual patients. Therapies that produce bronchodilation are now the mainstay of therapy; however, clinicians must decide whether to use a short- or long-acting agent, from which class to select, and whether or not combination therapy is appropriate.

## Key Points

- The systematic use of drugs as maintenance therapy to optimize pulmonary function in COPD, mainly bronchodilators and corticosteroids, began to gain popularity in the 1990s.
- COPD generally is classified into four stages based on the degree of airflow limitation measured by spirometry, providing a description of the severity of pathological changes.
- Later-stage disease often requires multiple treatment modalities including pharmacotherapy, pulmonary rehabilitation (exercise, nutrition counseling, patient education) and, in some cases, domiciliary oxygen therapy.
- The advent of long-acting  $\beta_2$  agonists and, more recently, the long-acting anticholinergic agent tiotropium has changed the way COPD is managed.
- The more severe the airway flow obstruction, the greater the benefit in terms of exacerbation reduction seen with maintenance-inhaled corticosteroid therapy.

TREATMENT OF COPD has evolved over the last 100 years. The term itself was coined in the 1960s to describe a spectrum of symptoms sharing common features of chronic bronchitis and emphysema.<sup>1</sup> At that time the only treatments for COPD were antibiotics for pneumonia, potassium iodide used as a mucus thinner, and combination oral products containing ephedrine, a small amount of theophylline, and a small amount of sedative to address the side effects of ephedrine.<sup>2</sup> Nonselective adrenergic bronchodilators inhaled via a hand-held rubber bulb nebulizer or, after 1956, via the newly introduced metered-dose inhaler, were used mainly as needed for rescue. Corticosteroids were not used and oxygen therapy and exercise were not emphasized.<sup>2</sup>

Pulmonary rehabilitation began to evolve in the

1960s; however, an emphasis on the importance of smoking cessation did not become a feature of management until the 1990s.<sup>2</sup> The systematic use of drugs to maximize pulmonary function, including bronchodilators and, to a lesser extent, corticosteroids, also began to gain popularity in the 1990s.<sup>2</sup>

Within the last two decades anticholinergic agents have been added to the armamentarium. Interestingly, plants with anticholinergic properties, such as *Atropa belladonna* and *Datura stramonium*, were used in the 19th century to treat asthma. In 1869 Hyde Salter in the *Lancet* recommended tincture of belladonna and Theodore Roosevelt, at the age of 10, smoked stramonium cigars for his asthma. In the second edition of Sir William Osler's *Principles and Practices of Medicine*, published in 1895, belladonna in solution form or

smoked as cigarettes, with or without tobacco, was recommended for asthma.

### Current Management Strategies

COPD is generally classified into four stages (Exhibit 1).<sup>3</sup> The stages are based on airflow limitation measured by spirometry, providing a description of the severity of pathological changes in COPD. All forced expiratory values (FEV<sub>1</sub>) values refer to post-bronchodilator FEV<sub>1</sub>.<sup>3</sup>

### Goals of Therapy

Avoidance of risk factors is the key to management in the early stages (stages 0–2). Smoking cessation is essential to prevent disease progression.<sup>4</sup> Later-stage disease generally requires multiple treatment modalities including pharmacotherapy, nutrition counseling, and patient education.<sup>3</sup>

The goals for effective management of COPD are

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat exacerbations
- Prevent and treat complications
- Reduce mortality
- Minimize side effects from treatment.<sup>3</sup>

### Most Commonly Used Agents

Prevention and control of symptoms and reduction in the frequency and severity of exacerbations can be achieved by pharmacological therapy.<sup>3</sup> Exhibit 2 outlines the most common medications used for the treatment of COPD.

Bronchodilators have long been the mainstay of therapy for COPD. Initially, short-acting  $\beta_2$  agonists

and theophylline and, subsequently in the late 1980s and early 1990s, the short-acting anticholinergic ipratropium—either alone or in combination with albuterol—were the drugs of choice. The advent of long-acting inhaled  $\beta_2$  agonists and, more recently, the long-acting anticholinergic agent tiotropium have changed the way COPD is managed. Finally, inhaled corticosteroids have emerged as potentially beneficial add-on therapies. It is still not clear whether a combination of two long-acting inhaled bronchodilators of different classes (i.e., a long-acting  $\beta_2$  agonist together with a long-acting anticholinergic bronchodilator) may have advantages over the combination of a long-acting  $\beta_2$  agonist and an inhaled corticosteroid.

### What the Studies Show

In the 1980s, studies were performed comparing the effects of short-acting  $\beta_2$  agonists and short-acting anticholinergics in both asthma and COPD.<sup>5,6</sup> In general,  $\beta_2$  agonists resulted in greater bronchodilation among asthmatics, whereas anticholinergics had superior results in patients with COPD. This is potentially because increased cholinergic tone is only one of the problems in asthma, whereas in COPD cholinergic tone appears to be the major cause of reversible airflow obstruction. Thus, in theory, single-agent therapy with an anticholinergic drug would seem appropriate for maximally reversing the reversible component of airflow obstruction in COPD by eliminating cholinergically mediated bronchomotor tone. However, this is only true if maximal doses are administered. Since this currently is not the case, there may be a rationale for adding a  $\beta_2$  agonist to achieve optimal bronchodilation.

A study investigating the effects of administering inhaled ipratropium plus albuterol versus albuterol or

Exhibit 1: Classification of Severity of COPD.<sup>3</sup>

Stage	Characteristics
0: At risk	<ul style="list-style-type: none"> <li>• Normal spirometry</li> <li>• Chronic symptoms (cough, sputum)</li> </ul>
I: Mild COPD	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt;70% (for stages I-IV)</li> <li>• FEV<sub>1</sub> ≥80% predicted</li> <li>• With or without chronic symptoms</li> </ul>
II: Moderate COPD	<ul style="list-style-type: none"> <li>• 50% ≤FEV<sub>1</sub> &lt;80% predicted</li> <li>• With or without chronic symptoms</li> </ul>
III: Severe COPD	<ul style="list-style-type: none"> <li>• 30% ≤FEV<sub>1</sub> &lt;50% predicted</li> <li>• With or without chronic symptoms</li> </ul>
IV: Very severe COPD	<ul style="list-style-type: none"> <li>• 30% ≥FEV<sub>1</sub> predicted or &lt;50% predicted plus chronic respiratory failure*</li> </ul>

FVC = forced vital capacity

\*Respiratory failure: PaO<sub>2</sub> <60 mm Hg, with or without PaCO<sub>2</sub> >50 mm Hg

**Exhibit 2: Commonly Used Drugs for the Treatment of COPD in the United States**

Drug	Short-acting	Duration of action (hrs.)	Long-acting	Duration of action (hrs.)
<b>β-agonists</b>	<ul style="list-style-type: none"> <li>• Terbutaline</li> <li>• Albuterol</li> <li>• Pirbuterol</li> </ul>	4 to 6	<ul style="list-style-type: none"> <li>• Formoterol</li> <li>• Salmeterol</li> </ul>	12+
<b>Anticholinergics</b>	<ul style="list-style-type: none"> <li>• Ipratropium bromide</li> </ul>	6 to 8	<ul style="list-style-type: none"> <li>• Tiotropium</li> </ul>	24+
<b>Combination long-acting beta-agonist plus anticholinergic in one inhaler</b>	<ul style="list-style-type: none"> <li>• Salbutamol/ipratropium</li> <li>• Albuterol/ipratropium</li> </ul>	6 to 8		
<b>Methylxanthines</b>	<ul style="list-style-type: none"> <li>• Aminophylline</li> <li>• Theophylline</li> </ul>			Variable, up to 6 Variable, up to 24
<b>Inhaled glucocorticoids</b>	<ul style="list-style-type: none"> <li>• Beclomethasone</li> <li>• Budesonide</li> </ul>	<ul style="list-style-type: none"> <li>• Fluticasone</li> <li>• Triamcinolone</li> </ul>	<ul style="list-style-type: none"> <li>• Flunisolide</li> </ul>	
<b>Combination long-acting beta-agonist plus glucocorticoids in one inhaler</b>	<ul style="list-style-type: none"> <li>• Salmeterol/fluticasone</li> </ul>			
<b>Systemic glucocorticoids</b>	<ul style="list-style-type: none"> <li>• Prednisone</li> <li>• Methylprednisolone</li> </ul>			

Reproduced with permission from NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary<sup>3</sup>

ipratropium alone revealed that although the combination produced greater bronchodilation, it had no additive effects on patient-centered outcomes, such as β<sub>2</sub> agonist use and symptoms.<sup>7</sup> The combination did, however, significantly reduce the number of exacerbations and hospitalizations compared to single therapy with albuterol, but not with ipratropium alone.

The popularity of theophylline, which translates as “tea leaf,” has waxed and waned over the years. With the advent of inhaled agents, it is now no longer routinely used, in part because it has only modest bronchodilator efficacy compared to inhaled agents. For example, in a study comparing this agent with ipratropium, the latter was more effective in increasing FEV<sub>1</sub> both at peak and over six hours.<sup>8</sup> However, theophylline may have a limited role as adjunctive therapy, as demonstrated in a study comparing the combination of this agent and albuterol versus ipratropium alone. In this study, a third arm examined the effect of combining all three agents: theophylline, ipratropium, and albuterol. The latter combination proved to be the most effective regimen.<sup>9</sup> On the other hand, in an earlier study ipratropium alone was superior

to the combination of the beta-agonist, fenoterol, and theophylline; although again, all three agents in combination produced the greatest bronchodilation.<sup>10</sup> A number of disadvantages associated with theophylline, including a narrow therapeutic-toxic window, not infrequent side effects (including some that are potentially serious, such as tachyarrhythmias and seizures) and several potential drug-drug interactions necessitating periodic monitoring of serum levels, have contributed to its fall from favor.<sup>11</sup>

Treatment algorithms for COPD have changed over the last decade with the introduction of twice-daily, long-acting inhaled β<sub>2</sub> agonists and the once-daily anticholinergic, tiotropium. Long-acting β<sub>2</sub> agonists have primarily been compared with placebo, rather than with ipratropium, the gold standard of therapy throughout the 1990s. However, in one study comparing salmeterol with ipratropium, the former was significantly better in improving lung function ( $P < 0.0001$ ) and increasing the time to first exacerbation ( $P < 0.05$ ).<sup>12</sup> However, Rennard and colleagues (2001) failed to achieve comparable results in a similarly designed study comparing salmeterol

with ipratropium. In another study, formoterol was significantly superior to ipratropium in increasing the area under the curve for FEV<sub>1</sub> ( $P<0.025$ ).<sup>13</sup> Compared with ipratropium, formoterol significantly improved symptoms ( $P=0.009$ ) and quality of life ( $P=0.002$ ) and reduced the mean daily number of puffs of a rescue  $\beta_2$  agonist ( $P<0.014$ ).<sup>13</sup>

The advent of tiotropium has added to the options available in the management of COPD. One advantage of tiotropium is that it results in bronchodilation that lasts at least 24 hours.<sup>14</sup> In a study comparing tiotropium with ipratropium, the former resulted in greater increases in FEV<sub>1</sub>.<sup>15</sup> The advantages of tiotropium are not confined to improved lung function, but also include reduction in albuterol use, improvement in dyspnea and quality of life, and reduction in exacerbations and time to first hospitalization.<sup>15</sup>

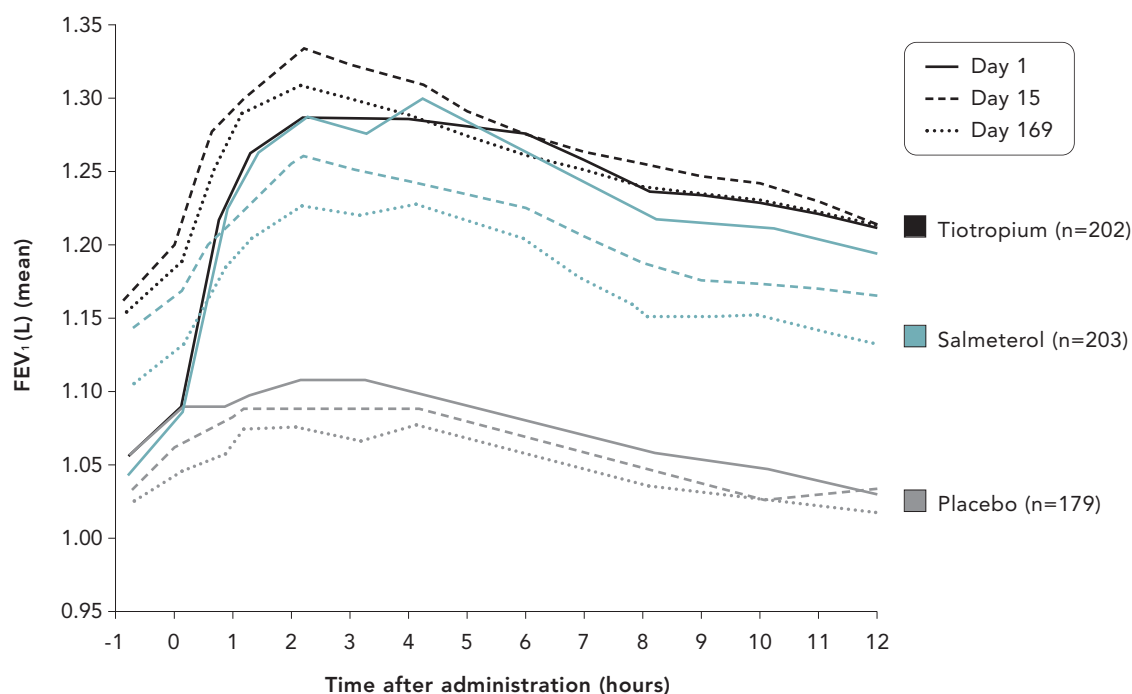
Tiotropium has been shown by Donohue and colleagues to result in increased FEV<sub>1</sub> over time compared with salmeterol (Exhibit 3).<sup>16</sup> In this study, tiotropium-treated patients statistically also experienced significantly greater improvements in dyspnea compared with salmeterol-treated patients ( $P<0.05$ ).<sup>17</sup>

In cases where one long-acting bronchodilator is not sufficient to optimize lung function, the most widely adhered to guidelines in the United States—

the Global Initiative for Chronic Obstructive Lung Disease (GOLD, developed by the National Heart Lung and Blood Institute and the World Health Organization)—recommend adding another long-acting inhaled agent.<sup>3</sup> Until recently there was no evidence from clinical trials to support this; instead, this recommendation was based on expert opinion. However, a study published in 2005 by van Noord and colleagues compared tiotropium plus placebo with tiotropium plus formoterol and with formoterol alone administered twice daily.<sup>17</sup> The addition of tiotropium to formoterol provided significant additive effects on lung function compared with those of either drug alone ( $P<0.05$ ). The improvement in FEV<sub>1</sub> continued throughout the night, despite the fact that formoterol was administered only once daily in the morning when given in combination with tiotropium.<sup>17</sup>

Data presented at the annual meeting of the American Thoracic Society in 2005 demonstrated that the combination of tiotropium and salmeterol significantly improves lung function compared with either drug alone ( $P<0.05$ ).<sup>18</sup> There is little evidence that inhaled corticosteroids alone slow the rate of decline in FEV<sub>1</sub> in patients with COPD.<sup>19-22</sup> However, they do reduce exacerbations.<sup>23</sup> The more severe the obstruction,

**Exhibit 3: Mean FEV<sub>1</sub> Before and After Treatment With Tiotropium, Salmeterol, and Placebo on Days 1, 15, and 169 of Treatment.<sup>16</sup>**



$P<0.001$  for tiotropium vs. placebo on all test days post treatment

$P<0.05$  for tiotropium vs. salmeterol on all test days except day 1 and -1h on day 15

the greater the benefit of inhaled corticosteroids with respect to reduction in exacerbations.<sup>24</sup>

Studies have shown that combining a long-acting  $\beta_2$  agonist and an inhaled corticosteroid has an additive effect on improvement in lung function.<sup>25,26</sup> However, the combination does not consistently show an additive effect on improvement in dyspnea or health-related quality of life, or on reduction in exacerbation frequency, or of the use of rescue medication.<sup>27,28</sup>

## Conclusions

The pharmacotherapy of COPD has evolved significantly over the last century. Because airflow obstruction is the main feature of COPD, therapies that produce bronchodilation have become the mainstay of therapy in patients who have persistent symptoms and experience exacerbations. The use of long-acting agents appears to be the best approach in this setting. **JMCM**

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# Pharmacology of Long-Acting Bronchodilators

Ronald J. DeBellis, PharmD, FCCP

## Summary

The two mechanisms of action by which pharmacologic agents work in treating bronchoconstriction utilize both the sympathetic and parasympathetic arms of the human nervous system. Bronchodilation has been predominantly associated with drugs that agonize receptors that are specific to achieving the adrenergic pharmacologic response of bronchodilation. This response becomes predominant in fight-or-flight situations. Conversely, agents that work on the parasympathetic nervous system have an anticholinergic effect on the lungs by blocking the action of acetylcholine produced by the vagus nerve. The vagus nerve is the predominant nerve that innervates the lung tissue. While at rest, acetylcholine is produced by the vagus nerve to cause bronchoconstriction. Instead of producing bronchodilation, these drugs are more accurately thought to inhibit bronchoconstriction.

## Key Points

- Both adrenergic and cholinergic influences result in the changeable lumen of the airway.
- The lung contains a significant concentration of  $\beta_2$ -adrenergic receptors.
- $\beta$ -adrenergic agonists stimulate  $\beta_2$ -adrenergic receptors and apparently have little or no effect on  $\alpha$ -,  $\beta_1$ -, or  $\beta_3$ -adrenergic receptors.
- Cholinergic tone is the primary reversible component of airway narrowing in chronic obstructive pulmonary disease (COPD).
- Administration of anticholinergic agents (ipratropium, oxitropium, and tiotropium) results in relaxation of airway smooth muscle.

THERE ARE TWO PATHWAYS that need to be reviewed when considering the use of bronchodilators in COPD. The first is the adrenergic, or sympathomimetic pathway, and the second is the cholinergic, or parasympathetic pathway.

### Adrenergic Pathway

$\beta$  adrenergic agonists stimulate  $\beta_2$ -adrenergic receptors and apparently have little or no effect on  $\alpha$ -,  $\beta_1$ -, or  $\beta_3$ -adrenergic receptors. The lung contains a significant concentration of  $\beta_2$ -adrenergic receptors. It is believed that  $\beta$ -adrenergic effects result from stimulation of the production of cyclic adenosine-3 prime, -5 prime, and -monophosphate (cAMP) by activation of the enzyme adenyl cyclase.

Numerous cellular responses appear to be mediated by cAMP. Increased concentrations of cAMP are associated with relaxation of bronchial smooth

muscle, suppression of some aspects of inflammation, and stimulation of lung ciliary function.

Salmeterol is a modification of the short-acting  $\beta_2$  agonist salbutamol.<sup>1</sup> It contains the saligenen head of salbutamol that binds to the active site of the  $\beta_2$ -adrenergic receptor, coupled to a long aliphatic side chain that increases the lipophilicity of the molecule.<sup>1</sup> Salmeterol diffuses laterally through the cell membrane to approach the  $\beta_2$ -adrenergic receptor. The side chain interacts with an auxiliary binding site (exo-site), a group of highly hydrophobic amino acids.<sup>1</sup> Binding to the exo-site prevents dissociation of salmeterol from the  $\beta_2$ -adrenergic receptor and allows the active saligenen head to repeatedly engage the active site of the receptor, accounting for the longer duration of action.<sup>1</sup>

The onset of action of salmeterol is within 20 to 30 minutes and the duration of action is approximately 12

**Exhibit 1: In Vitro Pharmacological Similarities and Differences between Salmeterol and Formoterol.<sup>1</sup>**

Smooth muscle cell preparations	
Membrane affinity	Salmeterol > formoterol
Duration	Salmeterol > formoterol
Selectivity	Salmeterol = formoterol
β-adrenergic receptor density	Salmeterol = formoterol
Onset	Formoterol > salmeterol
Potency	Formoterol > salmeterol
Efficacy	Formoterol > salmeterol

Inflammatory cells	
Human lymphocyte β-adrenergic receptor density	Salmeterol = formoterol
Inhibition guinea pig eosinophil activation	Formoterol > salmeterol
Inhibition human mast cell	Formoterol > salmeterol

hours. It is a maintenance medication and therefore is not used in the acute management of COPD.

Formoterol is a formanilide substituted phenoethanolamine, serendipitously found to be long acting when administered via inhalation.<sup>1</sup> The length of the side chain and resulting lipophilicity of formoterol is somewhere between that of salmeterol and salbutamol. The moderate lipophilicity of formoterol allows it to enter the plasmalemma and membrane to be retained.<sup>1</sup> The molecule then diffuses slowly to activate the β<sub>2</sub>-adrenergic receptor over an extended period. Sufficient drug remains available in the aqueous biophase to allow immediate interaction with the active site of the receptor, which accounts for its rapid onset of action.<sup>1</sup> The usual dose of formoterol is 12 mcg bid, administered via a dry powder inhaler. The onset of action is within one to three minutes; the duration of action is dose-dependent.<sup>2</sup>

In vitro, there are several pharmacological similarities and differences between salmeterol and formoterol (Exhibit 1).<sup>1</sup> However, the clinical relevance of in vitro differences remains to be established.

### Cholinergic Pathway

Cholinergic tone is chiefly responsible for primary airway narrowing in COPD. Bronchoconstriction is facilitated by acetylcholine. Administration of the anticholinergic bronchodilators (ipratropium, oxitropium, and tiotropium) results in relaxation of airway smooth muscle.<sup>3</sup>

Three types of muscarinic receptors are found in human airways.<sup>4</sup> M<sub>2</sub> and M<sub>3</sub> receptors are primarily responsible for mediating the bronchoconstrictor and mucus secretory response to acetylcholine and cholinergic nerve stimulation. Antagonism of these receptors results in the prevention of bronchocon-

striction.<sup>4</sup> Tiotropium binds to M<sub>3</sub> receptors with greater affinity than ipratropium, allowing for once-daily administration.<sup>5</sup> After inhalation, tiotropium reaches maximal plasma concentrations within five minutes, but clinical improvements in FEV<sub>1</sub> are maintained over 24 hours.

### Conclusions

There are clear differences in the mechanism of action of long-acting β<sub>2</sub> agonists and anticholinergic agents. The latter address the major reversible component of COPD—increased cholinergic tone. Ongoing research is attempting to better understand the mechanism of action of these agents as well as the disease itself to develop even more effective drugs. **JMCM**

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# Mechanisms and Treatment of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Sanjay Sethi, MD

## Summary

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) contribute to progression of disease, poor quality of life, increased health costs, and mortality. An exacerbation is defined as sustained worsening of a patient's condition beyond day-to-day variations, is acute in onset, and necessitates a change in regular medication. Approximately 80 percent of exacerbations are caused by viral and/or bacterial infection. Antibiotics should be chosen based on the risk severity of AECOPD.

## Key Points

- An exacerbation is defined as sustained worsening (at least 24 hours) of a patient's condition, is acute in onset, and necessitates a change in regular medication.
- Other causes, such as pneumonia, pulmonary embolism, and congestive heart failure should be ruled out by clinical evaluation.
- Fluoroquinolones appear to be effective in eradicating bacteria and certainly should be considered for use in complicated COPD.
- Several studies have demonstrated the benefits of oral corticosteroids in AECOPD in patients with underlying severe COPD; however, clinicians should be aware of the potentially serious adverse events associated with corticosteroids.
- Non-invasive ventilatory support (NIV) has proven to be extremely beneficial in patients with AECOPD.

ACUTE EXACERBATIONS of chronic obstructive pulmonary disease (AECOPD) contribute to progression of disease, poor quality of life, increased health costs, and mortality. Thus, it is crucial that clinicians understand the underlying mechanisms of exacerbations and are equipped with knowledge of how to recognize the symptoms and to treat them when they occur.

Generally an exacerbation is defined as sustained worsening of a patient's condition, beyond day-to-day variations. An exacerbation is acute in onset and necessitates a change in regular medication.<sup>1</sup> To be considered acute and sustained, symptoms should be present for at least 24 hours and the onset must be within two weeks. The most common symptoms of an exacerbation are an increase in dyspnea, sputum volume and/or sputum purulence.<sup>2</sup> It is important to note that these increased symptoms can have other

underlying causes which must be ruled out by clinical evaluation and selected use of diagnostic tests. These include pneumonia, pulmonary embolism, and congestive heart failure.<sup>1,3</sup>

## Mechanisms of Exacerbations

Exacerbations are caused by both infectious and non-infectious etiologies. Of the infectious etiologies, airway infection by bacteria, viruses, or a combination of the two, likely underlie up to 80 percent of properly diagnosed exacerbations.<sup>4</sup> Traditionally it has been thought that a viral infection occurs first, followed by bacterial infection. However, it is possible that chronic colonization with bacteria, by making the airway milieu more hospitable to infectious pathogens, can predispose patients to viral infection.

Acquisition of strains of bacterial pathogens new to the host is an important part of the pathogenesis of

bacterial exacerbations. The amount of resulting airway inflammation and consequent severity of symptoms depends on the virulence of the pathogen and the host lung defenses. Colonization by bacteria in the absence of increased symptoms still may be associated with increased airway inflammation, likely to a lesser extent than exacerbation.

Recurrent exacerbations may be associated with increased airway inflammation.<sup>5</sup> However, it is unclear whether this is cause or effect.<sup>6</sup> C-reactive protein (CRP), an inflammatory marker, has been shown to be a sensitive indicator of infections in a number of clinical situations, including acute pneumonia and infective exacerbations in cystic fibrosis patients.<sup>7</sup> CRP elevations have been observed in patients with exacerbations.<sup>7</sup>

### Treatment

There are a number of treatments for AECOPD, including bronchodilators, oxygen, antibiotics, and systemic corticosteroids. The most recent data available are from studies of antibiotics and corticosteroids.

The MOSAIC trial compared the effectiveness of moxifloxacin 400 mg once daily for five days with standard seven-day antibiotic regimens (amoxicillin [500 mg tid for seven days], clarithromycin [500 mg bid for seven days], or cefuroxime-axetil [250 mg bid for seven days]) as first-line therapy for infectious exacerbations of chronic bronchitis.<sup>8</sup> Patients were followed for up to nine months post-treatment. Although there were no differences in the primary outcome of clinical success, there was a significant difference in favor of moxifloxacin until approximately five months post-treatment in the time to first occurrence of a composite event comprising clinical failure, next exacerbation, or

need for further treatment (Exhibit 1).<sup>8</sup>

Antibiotics should be chosen based on a risk stratification basis, taking into account the severity of the exacerbation, the risks for failure of therapy based on underlying patient characteristics, and the risk of having an antibiotic-resistant pathogen as a cause of the exacerbation. Exhibit 2 shows an algorithm for selecting antibiotics according to patient risk.<sup>3</sup> The fluoroquinolones are more effective in eradicating bacteria and certainly should be considered for use in complicated COPD.

Several studies have demonstrated the benefits of oral corticosteroids in AECOPD.<sup>9-11</sup> One limitation of these studies is that they were performed in either the in-hospital or emergency room setting among patients with severe underlying COPD. Thus, it is not clear whether oral corticosteroids are of benefit and are necessary in exacerbations with better lung function treated in an outpatient setting.

When used, corticosteroids should be administered at a dose of 40 mg to 60 mg per day for seven to 14 days. Some clinicians recommend tapering the dose before discontinuation. Clinicians should be aware of the potentially serious adverse events associated with corticosteroids. In one study of invasive aspergillosis in non-immunosuppressed patients in an intensive care unit, patients with AECOPD who were treated with corticosteroids were the largest group.<sup>12</sup> Other potential side effects include hyperglycemia and steroid psychosis.

Non-invasive ventilatory support (NIV) has proven to be extremely beneficial in patients with AECOPD. The benefits include decreased intubation rates, shorter intensive care unit stays, decreased nosocomial infection, and decreased mortality.<sup>13-14</sup>

**Exhibit 1: MOSAIC Trial: Time to First Occurrence of Composite Event**  
(Clinical Failure, Next Acute Exacerbation of Chronic Bronchitis, or Need for Further Antimicrobial Treatment).<sup>8</sup>

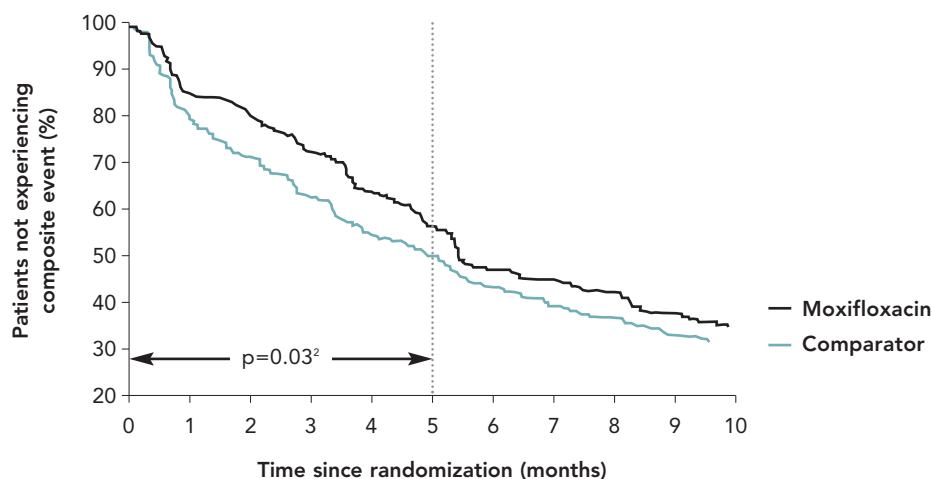
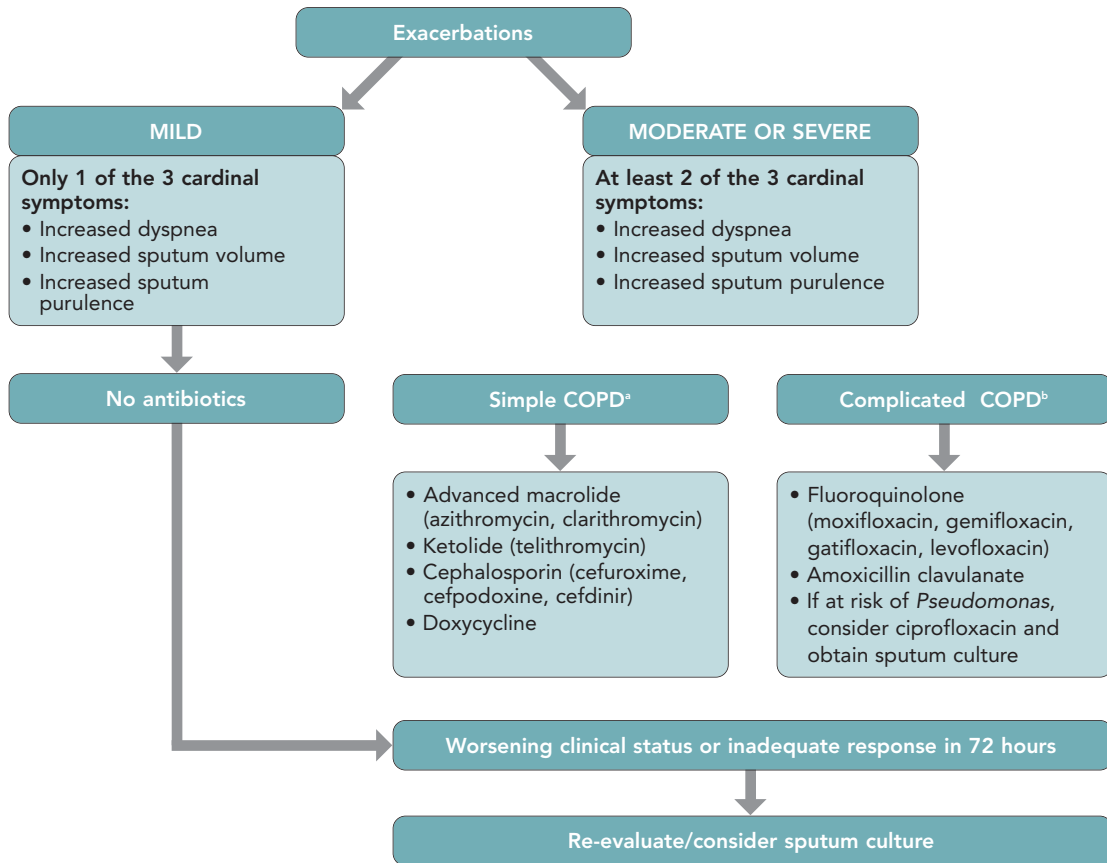


Exhibit 2: Risk Stratification of AECOPD.<sup>3</sup>



<sup>a</sup> No risk factors for poor outcome; no recent antibiotic therapy

<sup>b</sup> One or more of FEV<sub>1</sub> <50%, comorbid cardiac disease, three or more exacerbations in the previous 12 months, or antibiotic therapy in the previous three months

## Conclusions

AECOPD can have a negative impact on a patient's quality of living and disease progression and can also lead to increased healthcare costs. Careful definition of exacerbations facilitates rapid recognition and timely treatment. Because bacteria cause a substantial proportion of exacerbations, an understanding of how to stratify patients according to risk is important in ensuring that appropriate antibiotics are used. **JMCM**

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# Approach to Bronchodilator Therapy in the Hospitalized Patient with Chronic Obstructive Pulmonary Disease

Donald P. Tashkin, MD

## Summary

Patients with chronic obstructive pulmonary disease (COPD) in the hospital setting generally have more severe disease and are experiencing or are at risk of experiencing an exacerbation. The majority of published guidelines recommend treatment with a short-acting  $\beta_2$  agonist and/or ipratropium as first-line therapy for these patients. However, a number of studies in the outpatient setting suggest that combination therapy with long-acting agents for maintenance and short-acting agents as needed is more effective than short-acting bronchodilators alone. Further research is needed to determine whether such combination therapy has advantages over the use of short-acting bronchodilators alone in the hospital setting, and to identify the most appropriate delivery device(s) for aerosolized bronchodilators in hospitalized patients.

## Key Points

- Factors to be considered when choosing inhaled bronchodilators in hospitalized patients with COPD include dose and frequency, method of administration, and whether or not a long-acting agent is appropriate.
- The majority of guidelines currently recommend a short-acting  $\beta_2$  agonist and/or ipratropium.
- The role of aminophylline is controversial in the hospital setting.
- Meta-analyses show no significant differences between devices in their effects on lung function or symptoms in any patient group in any setting.
- In patients with COPD in the hospital setting, long-acting  $\beta_2$  agonists and the long-acting anticholinergic agent tiotropium offer several potential advantages.

SEVERAL FACTORS need to be considered when choosing which inhaled bronchodilator(s) to use in hospitalized patients with COPD. These include dose and frequency, method of administration and whether or not a long-acting agent is appropriate.

### Treatment Choice According to the Guidelines

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of short-acting  $\beta_2$  agonists<sup>1</sup> in the hospitalized patient. If a prompt response does not occur, the guidelines recommend adding ipratropium. This differs from the recommendations for outpatients with stable COPD, for whom anticholinergics are the drug of choice.<sup>1</sup>

The role of aminophylline in the hospital setting is controversial. However, according to the GOLD guidelines, the addition of an oral or intravenous

methylxanthine can be considered.<sup>1</sup>

The American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines recommend a short-acting  $\beta_2$  agonist and/or ipratropium via metered-dose inhaler with spacer or hand-held nebulizer as necessary.<sup>2</sup>

The Canadian Thoracic Society (CTS) guidelines, published in 2003, recommend combination therapy with a short-acting  $\beta_2$  agonist and short-acting anticholinergic agent.<sup>3</sup> Although the guidelines state that no difference has been shown between nebulized bronchodilators or those administered via a metered-dose inhaler with a spacer, they recommend using the latter mode of delivery because it is less expensive.<sup>3</sup> The guidelines do not recommend initiating methylxanthine therapy; however, they conclude that it is reasonable to continue this therapy if a patient already is receiving it, as

long as appropriate serum monitoring is performed.<sup>3</sup>

### Device Selection

The National Institute for Clinical Excellence guidelines developed in the United Kingdom suggest that both nebulizers and hand-held inhalers can be used to administer inhaled therapy.<sup>4</sup> The choice of the delivery system should reflect the dose of the drug required, ability of the patient to use the device, and the resources available to supervise therapy. If a patient is hypercapnic or acidotic, the nebulizer should be driven by compressed air, not oxygen. The guidelines further suggest that patients should be switched to hand-held inhalers as soon as their conditions stabilize.<sup>4</sup>

The American College of Chest Physicians and the American College of Asthma, Allergy, and Immunology have published guidelines on device selection based on a systematic review of randomized, controlled trials in which the same drug (bronchodilator or corticosteroid) was used with different devices in asthma or COPD in different settings (emergency room, inpatient, and laboratory).<sup>5</sup> None of the pooled meta-analyses showed significant differences between devices in their effects on lung function or symptoms in any patient group in any setting.<sup>5</sup>

### Combination Therapy

Various combinations of agents can be considered when prescribing more than one bronchodilator. However, there is little evidence available from clinical trials on the effectiveness of different combinations.

Kerstjens and colleagues studied the combination of tiotropium maintenance therapy plus two single doses of ipratropium or fenoterol or placebo in stable patients, administered six hours apart.<sup>6</sup> Compared with ipratropium alone, the combination of tiotropium and ipratropium resulted in significant improvements in FEV<sub>1</sub> ( $P<0.01$ ) both one hour post dose and at peak, as did the combination of tiotropium and fenoterol, a short-acting  $\beta$ -agonist. The latter combination was significantly more effective at improving FEV<sub>1</sub> than the combination of tiotropium and ipratropium at one hour post dose ( $P<0.01$ ) and at peak ( $P<0.0001$ ).

In a study of twice-daily maintenance salmeterol added to standard therapy in hospitalized patients with asthma, including systemic corticosteroids and frequent as-needed treatments with nebulized albuterol, the researchers found more rapid improvement in FEV<sub>1</sub> with the addition of salmeterol, but no significant difference in the time to discharge or the number of albuterol treatments required.<sup>7</sup> On the other hand, this study may not have been sufficiently powered to show a significant effect of the addition of maintenance therapy with salmeterol on the latter endpoints.

Campbell and colleagues studied the effectiveness of the long-acting  $\beta_2$  agonist formoterol, administered twice

daily as maintenance therapy, plus as-needed additional doses of formoterol, compared with maintenance formoterol, plus the short-acting  $\beta_2$  agonist terbutaline as needed, or placebo-plus-terbutaline as needed, in patients with stable COPD.<sup>8</sup> Both formoterol combinations significantly increased FEV<sub>1</sub> compared with placebo plus terbutaline as needed ( $P<0.01$ ).<sup>8</sup> In addition, symptom scores and need-for-rescue medication decreased significantly in both formoterol groups ( $P<0.01$ ). Importantly, no differences in adverse events or electrocardiographic findings were noted between the formoterol combination groups and placebo-plus-terbutaline PRN.<sup>8</sup> These findings support the safety and effectiveness of using a single long-acting inhaled  $\beta_2$  agonist both for maintenance and rescue therapy in stable COPD and have implications for the potential usefulness of this therapeutic strategy in the hospitalized patient with COPD. Additional studies evaluating the safety and effectiveness of this strategy in the in-patient management of acute exacerbations of COPD are warranted.

### Conclusions

In patients with COPD in the hospital setting, long-acting  $\beta_2$  agonists and the long-acting anticholinergic agent tiotropium offer several potential advantages. They may reduce the need for more frequent treatment with short-acting agents because of their sustained action, resulting in savings in personnel costs. They also may lead to greater overall improvement in lung function and potentially earlier discharge creating additional cost savings. Further studies are warranted to evaluate the possible benefits and risks of long-acting bronchodilators in the management of acute exacerbations of COPD in the hospital setting. **JMCM**

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# Pharmacoeconomic Impact of COPD in the Veterans Affairs Setting

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## Summary

Chronic obstructive pulmonary disease (COPD) is a common disease affecting veteran patients at a much higher rate than it does the general population. This disease imposes a substantial cost to the Veterans Affairs Health Care System (VAHCS), with an economic burden primarily related to inpatient care for acute exacerbations of COPD. The financial impact of COPD potentially could be reduced by strategic interventions with a capacity to reduce exacerbations and hospitalizations in the long term.

## Key Points

- COPD is a leading cause of disability among veterans.
- Although COPD is only the third most common chronic condition among Veterans Affairs (VA) patients, it carries with it the highest cost per patient per year.
- Hospitalizations for COPD account for 67 percent of VAHCS expenditures.

THERE IS A DISPROPORTIONATE burden of COPD among veteran patients when compared with the general population. The reported prevalence of COPD among veterans is 19 percent versus six to seven percent of the general population.<sup>1-3</sup> In fact, COPD is a leading cause of healthcare resource utilization among veteran patients<sup>4</sup> with an associated cost that is quite substantial for the VAHCS.

## A Look at the Numbers

COPD was responsible for \$37.2 billion in direct and indirect costs to the United States in 2004.<sup>5</sup> In the veteran population, this disease is among one of the top 10 chronic illnesses affecting patients.<sup>6</sup> This finding is not unique to the VAHCS. It has been reported that the cost of care for COPD Medicare beneficiaries increases 2.4 times compared to non-COPD Medicare beneficiaries (USD \$11,841 vs. \$4,901 in 2000).<sup>7</sup> Exhibit 1 shows a comparison of healthcare costs among non-COPD Medicare beneficiaries, COPD Medicare beneficiaries, and VA-COPD beneficiaries.<sup>6-8</sup> According to the Health Economics Research Center, hospitalizations for COPD account for up to 67 percent of VAHCS expenditures for this disease.<sup>6</sup> This is similar to the proportion spent among the general population on hospitalizations associated with COPD.<sup>3</sup> In contrast

to inpatient care, outpatient visits account for 24 percent of COPD-associated costs in the VAHCS, and prescription drugs account for only 8 percent of VAHCS expenditures.<sup>6</sup>

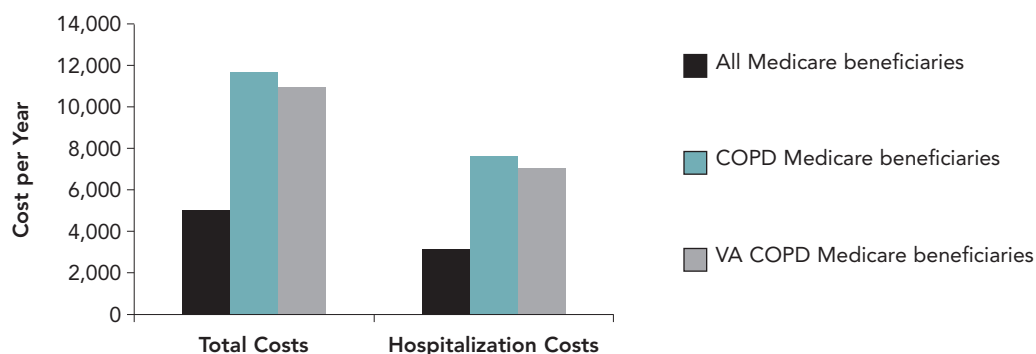
Patients with advanced COPD experience more frequent exacerbations<sup>2,9</sup> and frequent exacerbations often lead to hospitalizations.<sup>10</sup> Hospitalizations are the leading cause of healthcare expenditures in this disease, not only in the VAHCS but also among other healthcare systems.<sup>7,8,11</sup>

## Lessening the Economic Burden

Acute exacerbations of COPD frequently are experienced by patients with advanced disease, of whom a large proportion makes up the VA population. Recurrent acute exacerbations increase the risk for hospitalizations,<sup>10</sup> and result in poor health-related quality of life<sup>11</sup> and decrease survival.<sup>12-14</sup> Although treatment of COPD traditionally has been focused on symptomatic relief, it presently is accepted that pharmacotherapy and non-pharmacotherapy interventions have the potential to improve outcomes as well as symptoms, including reducing exacerbations and hospitalizations.<sup>12,13</sup>

Anticholinergic agents have been shown to play an important role in preventing exacerbations. The short-acting agent ipratropium reduces the

**Exhibit 1: Comparison of Year 2000 Healthcare Costs in U.S. Dollars Among All Medicare Beneficiaries, COPD Medicare Beneficiaries, and VA COPD Beneficiaries.<sup>6-8</sup>**



probability of exacerbations and the length of hospital stay compared with short-acting  $\beta_2$ -agonists.<sup>15</sup> More recently, a large study among veterans treated with tiotropium demonstrated a significant reduction in exacerbations and hospitalizations when compared to patients receiving placebo.<sup>16</sup> Long-acting agents are superior to short-acting ones, and constitute the preferred form of therapy for the maintenance treatment of COPD.

### Conclusions

It is clear that COPD presents a major burden to the VAHCS budget. The majority of cost relates to inpatient care for acute exacerbations of COPD while only 8 percent of the budget is spent on medications. Novel long-acting agents such as tiotropium may carry a higher acquisition cost; however, they are more effective at reducing exacerbations and hospitalizations. In addition, they have the potential to significantly impact the financial cost related to the treatment of COPD in the VAHCS should they be recommended as first-line therapy for this population of patients responsible for high utilization of healthcare resources. **JMCM**

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# Autonomic Nervous System Regulation of Airway Tone: Importance in COPD

Marvin Lesser, MD

## Summary

Airway smooth muscle is innervated by components of the autonomic nervous system. When activated, specific components are capable of markedly constricting bronchi or modulating dilation of a constricted airway. Thus, the autonomic nervous system performs a primary function in regulating airway tone. Dysfunction can presumably contribute to bronchoconstrictive components of airway diseases. Other features, including cough and dyspnea, also may be due to alterations in autonomic nervous system function.

## Key Points

- The autonomic nervous system modulates airway tone; secretion of mucus from submucosal glands; transport of fluid across the airway endothelium; permeability and blood flow in the bronchial circulation; and release of mediators from mast cells and other inflammatory cells.
- The parasympathetic system is the major autonomic component contributing to increased airway tone (bronchoconstriction) in humans and in all animal species.
- Decrease in airway tone is facilitated through interaction of epinephrine released from adrenal glands with  $\beta_2$  receptors and the inhibitory component of the NANC system.

A NUMBER OF FACTORS contribute to airway obstruction in COPD including neural influences, the contractile state of airway smooth muscle, thickness of airway walls, lung elastic recoil, mucus, and mucosal edema. Observations that subjects with COPD experience significant bronchodilation with anticholinergic agents suggest that cholinergic activity may be increased. A potential abnormality or abnormalities could exist in the parasympathetic, sympathetic and/or NANC components of the autonomic nervous system.

## Parasympathetic Nervous System

There is resting vagal tone in normal individuals to the level of terminal lung units. Stimulation of parasympathetic efferent cholinergic vagal pathways is the major cause of neurologically induced bronchoconstriction in all animal species. Efferent vagal output is influenced by centrally transmitted impulses by afferent nerves arising in the lungs, which include slowly adapting (stretch) receptors,

rapidly adapting (irritant) receptors, C-fiber endings, and, possibly, neuroendocrine cells.<sup>1</sup> Efferent-coded action potentials are carried in vagus nerves to autonomic ganglia located in airway walls.

Transmission in airway autonomic ganglia is complex and poorly understood. Modulation at the ganglia level is due to intricate anatomical, biochemical and electrophysiological characteristics of the ganglion neurons. Preganglionic release of neurotransmitter(s) is regulated by the transmitter itself, by other transmitters that are co-released or released from neighboring nerve terminals, by autocoids, and by activity-dependent mechanisms.<sup>2</sup> Neurotransmitter(s) released from preganglionic fibers activate nicotinic receptors and multiple excitatory and inhibitor cholinergic receptors on pre- and post-ganglionic membranes.<sup>2</sup> Rapid depolarization occurs through activation of nicotinic receptors and slow depolarization through activation of muscarinic M1 receptors.<sup>3</sup> Synaptic transmission is increased by tachykinins, antigen exposure, and

bradykinin.<sup>3</sup> Transmission is inhibited by presynaptic muscarinic autoreceptors and by  $\alpha$ -adrenergic heteroreceptors.<sup>3</sup> Acetylcholine release also may be modulated at the autonomic ganglia level by local release of norepinephrine from sympathetic nerves.

Release of acetylcholine from post-ganglionic nerve fibers at the level of airway smooth muscle is influenced by a number of factors at the pre-junctional levels including M2 autoreceptors, catecholamines, adrenoceptor agonists, prostaglandins, bradykinin, nitric oxide, and neurokinin A.<sup>3</sup> Acetylcholine-induced activation of M3 receptors is largely responsible for smooth muscle contraction. Muscarinic receptor-mediated signaling on airway smooth muscle cells is modulated by M2 receptors and  $\beta$ -adrenoceptors.<sup>3</sup>

### **Sympathetic Nervous System**

The adrenergic system is composed of sympathetic fibers that release norepinephrine at terminal endings, and the adrenal medulla, which secretes epinephrine, which functions as a circulating hormone.<sup>1</sup> Norepinephrine and epinephrine act through  $\alpha$ - and  $\beta$ -receptors. Sympathetic innervation of the lungs originates in the upper six thoracic segments of the spinal cord. Sympathetic nerve fibers synapse in the middle and inferior cervical ganglia, and in the upper four thoracic ganglia, and enter the hilum to intermingle with cholinergic nerves, where sympathetic fibers may modulate cholinergic neurotransmission in parasympathetic ganglia. Sympathetic fibers also innervate the smooth muscle layer of the human bronchial tree, with a few fibers reaching the level of secondary bronchi and terminal bronchioles.<sup>4</sup> Electron microscopic studies demonstrate close association of adrenergic nerves with smooth muscle cells.<sup>5</sup> In human lung it has been suggested that sympathetic nerves do not influence resting bronchomotor tone.<sup>1</sup> It is unknown if sympathetic nerves cause bronchodilation when bronchomotor tone is increased. Beta receptors located on airway smooth muscle cells are stimulated by circulating catecholamines. Epinephrine secreted by the adrenal medulla through interaction with  $\beta_2$  receptors located on airway smooth muscle cells is a potent factor contributing to a decrease in airway tone (bronchodilation).

### **Nonadrenergic Noncholinergic (NANC) Nervous System**

The NANC system consists of inhibitory and excitatory nerves that are components of the parasympathetic system. Nonadrenergic inhibitory nerves relax airway smooth muscle, thereby modulating bronchodilation. Activity appears to be

secondary to the release of nitric oxide and/or vasoactive intestinal peptide.<sup>6</sup> Noncholinergic excitatory nerves induce an increase in airway tone through release of the tachykinins substance P and neurokinin A, which interact with neurokinin-1 and neurokinin-2 receptors expressed by airway smooth muscle cells.

### **Non-Neuronal Cholinergic System**

Although generally considered a neurotransmitter, more recently it has been recognized that acetylcholine also is produced by epithelial cells, glandular tissue, smooth muscle cells, and migrating immune cells, including alveolar macrophages, granulocytes, and lymphocytes.<sup>7</sup> In addition, acetylcholine-sensitive muscarinic and nicotinic receptors are widely expressed on non-neuronal cells.<sup>7</sup> Therefore, acetylcholine acting through nicotinic and muscarinic receptors could modulate a number of cellular signaling pathways and modify or regulate various immune functions.<sup>7</sup>

### **Potential Abnormalities in COPD**

Observations of significant bronchodilatory responsiveness to anticholinergic agents among patients with COPD has led to the postulation that increased release of acetylcholine contributes to the pathogenesis of airway obstruction, particularly since parasympathetic, cholinergic nerves are predominantly responsible for increased airway tone in normal and abnormal lungs. In addition, abnormalities in the parasympathetic system could lead to increased cough sensitivity and greater mucus secretion, also of significance in COPD. Changes in the balance of rapidly adapting receptor and slowly adapting receptor input to the brain stem could be one mechanism for increased cholinergic bronchial smooth muscle tone in COPD.<sup>8</sup> Normally slowly adapting receptors inhibit parasympathetic preganglionic nerve activity.<sup>8</sup> This effect may be lost with modest elevations of  $\text{CO}_2$ .<sup>8</sup> Increasing the rate of respiration causes an increase in activity of rapidly adapting receptors.<sup>8</sup> Afferent neurotransmission also could be increased due to activation of bronchopulmonary C-fibers by inflammatory mediators including neuropeptides, cytokines and prostaglandins.

Another possible mechanism of increased cholinergic activity in COPD could be increased muscarinic receptor density or increased affinity of receptors for agonists. Muscarinic receptor number and function have been investigated among individuals with chronic airflow obstruction.<sup>9</sup> The number of receptors was measured by the binding of the radioactive muscarinic antagonist [3H]-(-)-

quinuclidinyl benzilate ([<sup>3</sup>H]-(-)-QNB). The affinity for agonists was investigated by studying the inhibition of [<sup>3</sup>H]-(-)-QNB binding by the full muscarinic agonist methylfurfurethionium. It was observed that muscarinic receptors in smooth muscle preparations of trachea, main bronchi, and segmental bronchial tissue preparations, which contained smooth muscle glandular tissue, were normal in density. These findings suggest unaltered muscarinic receptor characteristics in central airway smooth muscle of patients with chronic airflow obstruction. In a previous study it was determined that the number of binding sites was significantly less in peripheral lung homogenates of patients with chronic airflow obstruction.<sup>10</sup> These studies suggest that muscarinic receptor numbers may be modified in the small bronchi or at the alveolar level, whereas in the more central airways there is no change.

Other aspects of the cholinergic system have been investigated in obstructive lung disease. Activation of the excitatory component of the NANC system due to airway epithelial inflammation could be associated with release of neuropeptides, thereby contributing to bronchoconstriction and airway hyper-responsiveness. To investigate this system within the airways in asthma and chronic bronchitis, endobronchial biopsies were evaluated from 16 normal human volunteers, 49 patients with asthma of varying severity (including 16 patients treated with oral corticosteroids) and 13 patients with chronic bronchitis. Frozen sections of biopsies stained with specific antibodies against the neural marker PGP 9.5, vasoactive intestinal peptide, substance P, calcitonin gene-related peptide, and neuropeptide Y were assessed for the presence of nerves through indirect immunofluorescence.<sup>11</sup> Nerves were present in most of the biopsies and were found within and below the epithelium and adjacent to smooth muscle, glands, and blood vessels. By comparison with those in normal subjects, the number of vasoactive intestinal peptide-immunoreactive nerves was not significantly decreased in patients with asthma and chronic bronchitis. Neuropeptide Y-immunoreactive nerves were significantly decreased in the smooth muscle of patients with asthma and chronic bronchitis. The significance of these findings in COPD is unknown. There was no correlation between disease severity and the number of nerves found in the biopsies.

Among asthmatics there is evidence that M2 receptors are dysfunctional.<sup>12</sup> Reduced M2 receptor function leads to increased release of acetylcholine and enhanced bronchoconstriction. In animal studies, M2 dysfunction has been associated with viral infection, ozone exposure and antigen

challenge.<sup>12</sup> However, in a study of subjects with COPD, M2 muscarinic receptors were found to be functional in stable disease.<sup>13</sup> It is unknown if M2 muscarinic receptors are dysfunctional during acute exacerbations of COPD.

Autonomic ganglia represent a major site of integration of vagal transmission. Transmission is modulated by neurochemical, anatomical, and electrophysiological factors and is poorly understood. It is unknown if autonomic ganglia function is abnormal in COPD. Also, prejunctional regulatory mechanisms are complex. It has been suggested that impaired prejunctional inhibition, as well as augmented prejunctional facilitation, could lead to enhanced release of acetylcholine and that there is evidence based upon *in vitro* and animal studies that both mechanisms may contribute to bronchoconstriction in obstructive airway diseases.<sup>3</sup>

Amplified responsiveness to an anticholinergic agent in COPD could be due to geometric factors. Resistance to flow in conducting airways is inversely related to the fourth power of the radius. Therefore, already constricted airways due to a number of processes including mucus hyper-secretion, airway wall thickening, and decreased elastic recoil could manifest greater relative responsiveness to bronchomodulatory agents compared to the same degree of dilatation or constriction elicited in airways of normal caliber.

The importance of the non-neuronal cholinergic system in COPD is unknown. Enhanced levels of acetylcholine have been shown to stimulate an increase in glandular and smooth muscle activity *in vitro*.<sup>7</sup> The high number of muscarinic M2 receptors expressed on smooth muscle fibers may represent a target for the action of non-neuronal acetylcholine, which might directly interfere with the contractile response.<sup>7</sup> Muscarinic receptor antagonists will affect the actions of both neuronal and non-neuronal acetylcholine. It has not been determined if the non-neuronal cholinergic system contributes to airway dysfunction in COPD. An evaluation of the effects of treatment with tiotropium on airway smooth muscle changes in a guinea pig model of ongoing allergic asthma revealed that the long-acting muscarinic receptor antagonist inhibited the increase in airway smooth muscle mass, myosin expression, and contractility.<sup>14</sup>

## Conclusions

The contractile state of airway smooth muscle, thickness of the airway walls, lung elastic recoil, mucus hyper-secretion, and mucosal edema are the primary determinants of airway obstruction in COPD. It is unknown if baseline airway contraction

exists in COPD due to autonomic nervous system dysfunction and no specific “defect” in autonomic nervous function has been identified. The contribution of acetylcholine to airway remodeling is unknown at the present time but requires further investigation. JMCM

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# Novel Therapeutic Interventions for the Treatment of COPD

Thomas J. Ferro, MD

## Summary

Chronic obstructive pulmonary disease (COPD) attracts a great deal of research attention. Ongoing research into a number of novel therapeutic modalities will, it is hoped, address areas of controversy and produce favorable results. For example, the debate continues as to whether systemic corticosteroids should be an integral part of a COPD regimen, although there is evidence that these agents can improve outcomes. The addition of tiotropium, a long-acting anticholinergic agent, to the pharmacological armamentarium offers clinicians another option in their efforts to manage COPD.

## Key Points

- Because of its long half-life, tiotropium offers once-daily dosing.
- In McGuire Veterans Affairs Medical Center patients with moderate-to-severe COPD, tiotropium reduces exacerbations and attendant healthcare utilization by approximately 20 percent.
- If prescribed, systemic corticosteroids should only be administered for short periods of time to avoid unwanted systemic effects.
- Researchers are investigating a number of novel agents for use in COPD.

OVER THE LAST DECADE researchers have been investigating a number of pharmacological approaches to the management of COPD. Tiotropium, a long-acting anticholinergic agent, is a result of this research. Other areas of investigation include the place of corticosteroids (inhaled and systemic) and the potential role of selective phosphodiesterase inhibitors, mucolytics, and antioxidants.

## Tiotropium

Until recently, ipratropium bromide was the only inhaled anticholinergic available to patients with COPD in the United States. In January 2004, tiotropium bromide inhalation powder received marketing approval from the FDA for the long-term treatment of bronchospasm associated with COPD.

After inhalation, tiotropium reaches maximal plasma concentrations within five minutes; however clinical improvements in FEV<sub>1</sub> are maintained for over 24 hours.<sup>1,2</sup> Clinical trials of tiotropium compared with placebo, ipratropium, salmeterol, and formoterol have demonstrated the efficacy of tiotropium in improving FEV<sub>1</sub>, forced vital capacity (FVC) values, and health-related quality of life.<sup>3-7</sup>

The most frequently reported adverse effect with tiotropium is dry mouth, which occurs in up to 16 percent of patients.<sup>1</sup> Other adverse effects, such as constipation, tachycardia, and blurred vision, also have been reported.<sup>1</sup> Cautious use of tiotropium is recommended in patients with conditions that could be exacerbated by the addition of an anticholinergic agent, such as benign prostatic hyperplasia and glaucoma.<sup>1</sup>

## In the Veterans Affairs Setting

Tiotropium has been studied in a large-scale, randomized, double-blind, placebo-controlled trial in the Veterans Affairs (VA) setting.<sup>8</sup> In this study, 1,829 patients with moderate to severe COPD (FEV<sub>1</sub> 36 percent) were randomized to once-daily tiotropium 18 mcg or placebo for six months. Patients also received usual care, with the exception of other inhaled anticholinergic agents.<sup>8</sup> The primary endpoints were the percentage of patients with an exacerbation and the percentage with a COPD-related hospitalization.<sup>8</sup>

Compared with placebo, tiotropium significantly reduced the percentage of patients experiencing

one or more exacerbations (Exhibit 1).<sup>8</sup> Fewer patients treated with tiotropium were hospitalized with an exacerbation compared with patients in the placebo group (7 percent vs. 9.5 percent;  $P=0.056$ ). Compared with placebo, tiotropium significantly reduced the number of antibiotic days per patient year (8.1 days vs. 9.8 days;  $P=0.015$ ); the number of COPD-related emergency department visits per patient year (0.39 visits vs. 0.49 visits;  $P=0.019$ ); and the number of COPD hospitalizations per patient year (0.18 hospitalizations vs. 0.25 hospitalizations;  $P=0.047$ ).<sup>8</sup>

The authors concluded that in VA patients with moderate-to-severe COPD, tiotropium reduces exacerbations and attendant healthcare utilization by approximately 20 percent.<sup>8</sup>

### Corticosteroids—Ongoing Debate

When considering the use of corticosteroids in COPD, clinicians need to consider two aspects of treatment. First is whether the patient has stable disease or whether he or she is experiencing an exacerbation. Second is which mode of administration is most appropriate.

In patients with chronic stable disease, it has been demonstrated that inhaled corticosteroids do not slow the rate of decline in lung function; however, they have been shown to improve airway reactivity and respiratory symptoms and decrease the use of healthcare services for respiratory problems.<sup>9</sup> These benefits need to be weighed against the adverse effects that these agents can have on bone mineral density.<sup>9</sup>

In patients with acute exacerbations of COPD, short courses of oral or intravenous corticosteroids have been shown to improve both spirometric and clinical outcomes. In a double-blind, randomized,

placebo-controlled trial, patients with acute exacerbations who presented to the emergency department were randomized to receive either a 10-day course of 40 mg of prednisone or placebo.<sup>10</sup> Prednisone decreased the risk for relapse by nearly 40 percent and led to improved dyspnea scores and lung function.<sup>10</sup>

In a study of a more severely ill, hospitalized group, patients were randomized to treatment with either methylprednisolone 125 mg intravenously every six hours, or placebo.<sup>11</sup> Patients in the steroid arm then were treated with either two or eight weeks of oral corticosteroids. Patients in the corticosteroid arm had more rapid improvements in FEV<sub>1</sub>. These patients also had fewer treatment failures and were discharged from the hospital an average of one day sooner than those in the placebo group.<sup>11</sup> The extension of oral corticosteroids for eight weeks conferred no improvements over the shorter two-week course. However, the longer treatment regimen led to more side effects, such as hyperglycemia.<sup>11</sup> A meta-analysis by Singh and colleagues demonstrated that a number of well-designed studies are consistent with the findings presented above.<sup>12</sup>

### Under Investigation

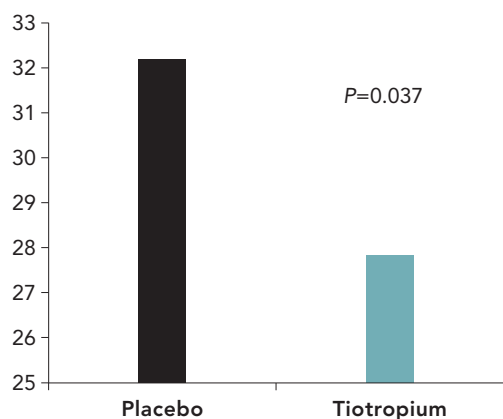
A number of lines of research are being followed in the quest for improved treatments for COPD. Several once-daily  $\beta_2$  agonists are being studied, as well as additional long-acting anticholinergic agents.

Combination therapy is receiving a great deal of attention. However, it is not yet clear which combinations of existing agents will prove most effective, both clinically and from a cost perspective.

Researchers also are investigating the potential use of “safer” steroids, such as the pro-drug ciclesonide, which has been studied in asthma. Investigators also are examining so-called “dissociated glucocorticoid receptor agonists,” which apparently offer the anti-inflammatory benefits of steroids without the unwanted systemic effects.

Novel anti-inflammatory therapies are being developed as potential therapeutic agents. Phosphodiesterase inhibitors (PDEs) have significant anti-inflammatory and bronchodilatory effects. Of selective PDEs, the most widely studied to date are cilomilast and roflumilast.<sup>13</sup> Short-term trials with these agents have demonstrated important anti-inflammatory effects associated with an improved therapeutic ratio when compared with nonselective PDE inhibitors such as theophylline.<sup>13</sup> Although improvement in lung function is modest with the use of these agents, their anti-inflammatory effects may provide benefits in reducing exacerbations and improving health-related quality of life.<sup>13</sup>

**Exhibit 1: VA Tiotropium Trial—Percentage of Patients Experiencing One or More Exacerbations.<sup>8</sup>**



Oxidative stress is increased in patients with COPD, particularly during exacerbations. Thus, antioxidant agents are being studied in this area. The results of the first long-term trial of the antioxidant agent N-acetylcysteine were not promising.<sup>14</sup> There were no differences between patients treated with N-acetylcysteine and those in the placebo group in the rate of decline in lung function over the three years of the trial; nor were there any differences in exacerbation rates between the groups.<sup>14</sup>

Multiple leukotriene  $\beta_4$  antagonists, which, among other effects, inhibit neutrophil chemotaxis, are in development. Although several agents are approved for use in asthma, the role of these agents in COPD remains unclear. One antagonist that has been studied in asthma—LY 293111—does not prevent exacerbations, although it inhibits the mobilization of neutrophils, indicating it may have a place in the treatment of COPD.<sup>15</sup> The leukotriene antagonist zafirlukast has been studied in COPD with negative results.<sup>16</sup> However, marketing data suggest that these agents are sometimes used in patients with COPD.

## Conclusions

Ongoing research is extensive in the field of COPD. Tiotropium is the first long-acting anticholinergic to be approved and offers clinicians an attractive option for the management of patients with COPD. The role of systemic corticosteroids is still often debated; however, short courses of these agents appear to have a role in symptom reduction. A number of other treatments are being investigated and it is hoped that this research will result in agents that will further optimize COPD management. **JMCM**

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# Case Study: The Deteriorating Patient

Douglas B. Schwartz, MD

## History

A 73-year-old man presented with increasing breathlessness on exertion. His condition was gradually deteriorating without any precipitating causes, such as an exacerbation. He was a prolific cigarette smoker with a long history of a chronic productive cough. In recent years, he had been treated for one to two acute exacerbations of chronic obstructive pulmonary diseases (AECOPD) annually. He was being treated with a combination agent composed of ipratropium and albuterol (Combivent®) at a dose of two puffs with spacer, prescribed to be used five times daily. However, he reported that he used it three times daily when he needed it.

## Examination

On examination, his FEV<sub>1</sub> was 60 percent and his forced vital capacity (FVC) was 55 percent. There were no changes in his sputum volume or chronic cough and no signs of fever, chills, rigors, sweats, orthopnea, or postnasal drainage. His respiratory rate was 24 breaths per minute. Decreased breath sounds and prolonged forced expiratory maneuver were noted. There was a trace of pre-tibial edema. His chest X-ray revealed hyperinflation of the lungs, no infiltrates, and no cardiomegaly.

## Management Issues

There are a number of questions to be answered when managing a patient with COPD whose condition is gradually deteriorating.

- What is the optimal mode of administration?
- Should this patient be considered a Combivent® failure?
- Is a role for a long-acting bron-

chodilator or combination of two of these agents present in this patient?

- Should Combivent® be retained as a rescue agent?
- Should the components of Combivent® be administered separately? For example, should ipratropium be administered with a long-acting  $\beta_2$  agonist?
- Should ipratropium be used in combination with tiotropium?
- What is the role of corticosteroids?
- Is there a role for the combination agent composed of fluticasone and salmeterol (Advair®)?
- What is the patient's history of compliance with multiple medications?

## Treatment

This patient is an ideal candidate for tiotropium. However, current VA guidelines prohibit the use of tiotropium unless a patient has failed Combivent®. In this case, the clinician was able to prescribe tiotropium once daily, which was obtained by using a nonformulary drug request consultation. Ipratropium, two puffs via spacer, was used for a week after tiotropium was initiated. He also was prescribed formoterol twice daily. One to two puffs of albuterol with chamber every six hours was prescribed as rescue medication. The patient felt slightly better after one month and was able to assist his wife with household chores after three months.

## Conclusions

Patients with deteriorating COPD present a number of challenges to clinicians practicing in the VA system. The current VA guidelines are somewhat restrictive; thus, clinicians must be somewhat inventive in the methods that they use to ensure patients receive optimal care. **JMCM**

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# Case Study: Severely Ill Patients

Shelia Goodnight-White, MD

## History and Examination

A 65 year-old-male presented with chronic shortness of breath despite using scheduled short-acting bronchodilators. He started smoking at age 16 and stopped one year prior to presentation. Breathlessness began at age 50. His lungs were hyperinflated. Pulmonary function testing revealed a forced expiratory volume in 1 second (FEV<sub>1</sub>) of 0.9L (27% of predicted normal value) and an FEV<sub>1</sub>/forced vital capacity (FVC) ratio of 25%. Computerized axial tomography (CAT) scan revealed relatively diffuse emphysema that was more pronounced in the lower lobes.

## Management and Follow-up

In 2000, this patient requested evaluation for inclusion in a trial investigating lung volume reduction surgery (LVRS). He was enrolled in the trial and underwent six weeks (18 sessions) of pulmonary rehabilitation. He was randomized to the medical arm to receive "usual medical care" and was followed for 36 months. His initial medications comprised short-acting bronchodilators and he was administered oxygen during exercise and nocturnally. His condition was relatively stable at this time. He experienced two exacerbations but remained employed. After two years, his primary care physician added fluticasone/salmeterol (Advair®) due to a decline in FEV<sub>1</sub>, increased symptoms, and an exacerbation.

Results of National Emphysema Trial (NETT)<sup>1</sup>, published subsequently in 2003, revealed that this patient would be a poor candidate for LVRS.<sup>1</sup> The study demonstrated

that although LVRS may increase the chance of improved exercise capacity, pulmonary function, and quality of life in appropriately selected patients, it does not confer a survival advantage over medical therapy in all patients. Patients with both predominantly upper-lobe emphysema and baseline low exercise capacity treated surgically have a survival advantage. However, patients, such as this man with non-upper-lobe emphysema and baseline high exercise capacity, are poor candidates for LVRS. Investigators identified increased mortality and negligible functional gain in these patients.<sup>1</sup>

Pulmonary function results for this man over the next four years showed FEV<sub>1</sub> stabilization. He continued to benefit from pulmonary rehabilitation; the distance he was able to walk in six minutes (6MWD) was greater than baseline. Four years after presentation, his FEV<sub>1</sub> was 0.85 L (23 percent of predicted value) and he required oxygen supplementation continuously. Tiotropium was added. He experienced symptomatic improvement. One year after tiotropium institution, using tiotropium daily, salmeterol/fluticasone twice daily and albuterol as necessary, his FEV<sub>1</sub> increased to 1.13 L (33 percent of predicted normal value); he had returned to baseline exercise, such as playing golf, and required oxygen supplementation only at night and with exercise.

### Conclusions

Lung volume reduction surgery can be considered in those suffering with severe COPD. Careful patient selection is crucial when contemplating surgical intervention. Pulmonary rehabilitation improves durable outcomes. Medication optimization improves symptoms and increases exercise capacity, even in those with severe airflow obstruction and diffuse parenchymal destruction. **JMCM**

Sheila Goodnight-White, MD, is associate professor of medicine at Baylor College of

Medicine and chief of pulmonary and clinical care medicine at the Michael E. De Bakey Veterans Affairs Medical Center in Houston.

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## Case Study: Managing Acute Exacerbations

Joel B. Karlinsky, MD, MBA

### History and examination

A 68-year-old man presented to an emergency department with shortness of breath of one day's duration. He had a history of a severe chronic obstructive pulmonary disease (COPD) with an FEV<sub>1</sub> of 0.48 liters, and had sustained a left lower lobectomy in 1991 for bronchogenic carcinoma *in situ*. The patient was maintained on home oxygen and was wheelchair bound. His past medical history included coronary artery disease, congestive heart failure, hypertension, anemia of chronic disease, hyperlipidemia, diabetes mellitus type 2, benign prostatic hyperplasia, and osteoporosis. The patient had experienced multiple recent hospital admissions for exacerbations of COPD, his most recent having been for treatment of right lower lobe pneumonia a month earlier. He had been discharged to a pulmonary rehabilitation facility in stable condition.

Since discharge the patient had experienced worsening dyspnea on exertion. In the emergency department he was noted to have an oxygen saturation of 82 percent on two liters nasal cannula and pursed-lip breathing. The patient was transferred to the Boston VA Medical Center emergency department where an arterial blood gas revealed

a pO<sub>2</sub> of 55 Torr and a pCO<sub>2</sub> in the eighties. The patient was placed on a 50 percent ventimask. His oxygen saturation initially improved to 94 percent, but subsequently decreased to 66 percent. He was then transferred to the medical intensive care unit, where a portable chest film revealed worsening of his right lower lobe process.

### Management

The patient was treated with nebulized albuterol/ipratropium every two hours. Systemic steroids (Dexamethasone 4mg IV every six hours), fluticasone, and antibiotics covering *Pseudomonas aeruginosa* (his last known organism) were administered. However, the patient did not improve. His oxygen saturation remained in the 60 percent range on five liters of oxygen and BiPAP. Culture results revealed *Pseudomonas aeruginosa*.

Morphine, at a dose of 1-2 mg, was administered three to four times daily to relieve dyspnea. BiPAP was continued. Two days post admission to the MIC, his oxygen saturation was 92 to 94 percent and the patient remained extremely dyspneic and hypercarbic. Tiotropium was begun. Two days later, his dyspnea and oxygenation were much improved. BiPAP was discontinued; the patient was transitioned to oral steroids; and he then could be maintained on oxygen administered via a nasal pendant. Oxygen saturation levels were 96 to 98 percent. Antibiotics were continued and the patient was transferred to the medical ward one day later. Intubation and mechanical ventilation were averted.

### Conclusions

Severely ill patients with exacerbations are frequently admitted to an intensive care unit. Initiation of therapy with a long-acting bronchodilator can reduce the risk of the need for intubation in these

patients. To avoid hospitalization, patients who present with an exacerbation potentially may be treated initially with a long-acting bronchodilator, antibiotics, and steroids, and seen again the next day in the outpatient clinic to assess their status. **JMCM**

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## Case Study: When Is it Best to Start Long-Acting Bronchodilators?

Thomas J. Ferro, MD

### History

A 78-year-old man with multiple medical problems including a six-year history of chronic obstructive pulmonary disease (COPD), a ratio of FEV<sub>1</sub> to forced vital capacity (FVC) <70 percent, and absolute FEV<sub>1</sub> 49 percent of predicted, was seen in the pulmonary clinic at the local Veterans Affairs (VA) medical center for hemoptysis. In addition to hemoptysis, the patient complained of dyspnea on exertion, which had become slightly worse over the past year. He had been treated for two episodes of acute worsening of dyspnea and other respiratory symptoms during the past year, one as an outpatient and one as an inpatient. He was compliant with his medications, which included ipratropium/albuterol metered-dose inhaler, eight to 12 puffs per day. Flexible fiberoptic bronchoscopy revealed a tracheal adenoma, which was not biopsied to avoid the possibility of uncontrollable hemoptysis. The patient was much more dyspneic after the

procedure, with decreased breath sounds and wheezing bilaterally. A chest roentgenogram was unchanged from the pre-procedure baseline.

### Treatment

The patient was admitted to the hospital with the diagnosis of acute exacerbation of COPD. He was given his usual medications, except that the ipratropium/albuterol metered-dose inhaler was discontinued, and albuterol plus ipratropium via nebulization every four hours and prednisone 40 mg by mouth daily were started. Orders also were written for an inhaled corticosteroid and tiotropium inhaler.

### Discussion

The administration of both the inhaled corticosteroid and tiotropium required further discussion. Pharmacy questioned the need for the initiation of these treatments during hospitalization, and also expressed concern that the tiotropium was redundant with the ipratropium. After some deliberation, the medications were dispensed and administered.

The patient met criteria for the use of both the inhaled corticosteroid and tiotropium even before the fiber-optic flexible bronchoscopy (FFB), because he had advanced COPD and was having infrequent exacerbations. These agents both are associated with a significant reduction in exacerbation risk and quality-of-life improvement in patients with advanced COPD, and tiotropium also is associated with improved lung function and exercise performance. The use of these medications might have prevented the post-FFB bronchospasm and exacerbation. The initiation of these drugs during the hospitalization was intended to avoid the possibility that these medications would again be overlooked in the complex

process of planning this patient's multi-drug regimen.

Further rationale exists for the in-hospital combination of the short-acting anticholinergic ipratropium and the long-acting anticholinergic tiotropium during the initiation of tiotropium therapy. Tiotropium is believed to provide at least as much benefit as ipratropium during an acute exacerbation of COPD, based on its anticholinergic effect. However, this presumed benefit requires that the patient has been on the tiotropium for at least one week so that its effect is steady state. During the period of acute exacerbation, if the patient has not been on tiotropium long enough to achieve steady state, it probably is wiser to continue the ipratropium. After about one week, if the tiotropium has been taken properly, the ipratropium can be discontinued. Once the patient is at steady state for tiotropium effect, the drug simply can be continued as the sole anticholinergic during the next acute exacerbation. **JMCM**

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# Consensus Report: Optimizing the Use of Long-Acting Bronchodilators in the Veterans Affairs Healthcare System

Thomas J. Ferro, MD; Claudia G. Cote, MD, FCCP; Ronald J. DeBellis, PharmD, FCCP;  
Sheila Goodnight-White, MD; Joel B. Karlinsky, MD, MBA; Marvin Lesser, MD;  
Julio A. Ramirez, MD; Douglas B. Schwartz, MD; Sanjay Sethi, MD; Donald P. Tashkin, MD

## Summary

Current Veterans Affairs (VA) guidelines for the management of chronic obstructive pulmonary disease (COPD) restrict the use of long-acting inhaled bronchodilators. However, scientific data and national guidelines indicate that patient outcomes may be improved by use of these newer agents. VA providers can optimize patients' outcomes by using these agents whenever indicated in accordance with scientific data and national guidelines as reviewed here.

## Key Points

- Current VA guidelines for the use of long-acting bronchodilators are restrictive, necessitating providers to utilize "older" agents and document poor outcomes prior to utilizing "newer" novel agents.
- Familiarity with national guidelines and evidence-based data concerning the benefit of these agents is essential to providing veterans with optimal patient care.
- Outcomes of COPD patients treated in the VA system are likely to improve if providers use newer long-acting bronchodilators as a key component of the treatment regimen for symptomatic patients with moderate-to-severe disease.
- VA guidelines are currently under review.

COPD IS ASSOCIATED with significant health and socioeconomic burdens. This is particularly true among the VA population, for which COPD accounts for the highest per-patient expenditure annually. Treatment strategies should, optimally, be designed to reduce dyspnea and COPD exacerbations, which result in patient morbidity and hospital admissions.

The Global Initiative for Obstructive Lung Disease (GOLD) and the American Thoracic Society (ATS)/European Respiratory Society (ERS) have published guidelines that reflect evidence-based medicine and current best practices for the management of COPD. We suggest that these guidelines should form the basis for management of COPD among patients in the VA healthcare system.

Both the GOLD and ATS/ERS guidelines recommend that a short-acting bronchodilator be

used regularly or as necessary for short-term relief of dyspnea at the earliest stages of the disease.<sup>1,2</sup> The guidelines do not recommend a specific type of short-acting bronchodilator (i.e., an anticholinergic or  $\beta_2$ -agonist).

The GOLD panel recommends the addition of long-acting inhaled bronchodilators for patients with moderate to severe symptomatic COPD (Exhibit 1).<sup>1</sup> For patients with stage 1 COPD and intermittent symptoms, short-acting bronchodilators, used when needed, will reduce dyspnea. In patients with stage 2 to stage 4 COPD, the GOLD panel recommends adding treatment with a long-acting inhaled bronchodilator to the therapeutic regimen.<sup>1</sup>

Patients with moderate to very severe COPD with persistent dyspnea despite taking a short- or long-acting inhaled bronchodilator on a regular basis also may benefit from the addition of a second bronchodilator that acts by a different

mechanism. Lastly, patients with stage 3 and 4 COPD and repeated exacerbations despite optimal bronchodilator therapy may benefit from the addition of regular treatment with inhaled corticosteroids.<sup>1</sup>

The ATS and the ERS have adopted a similar

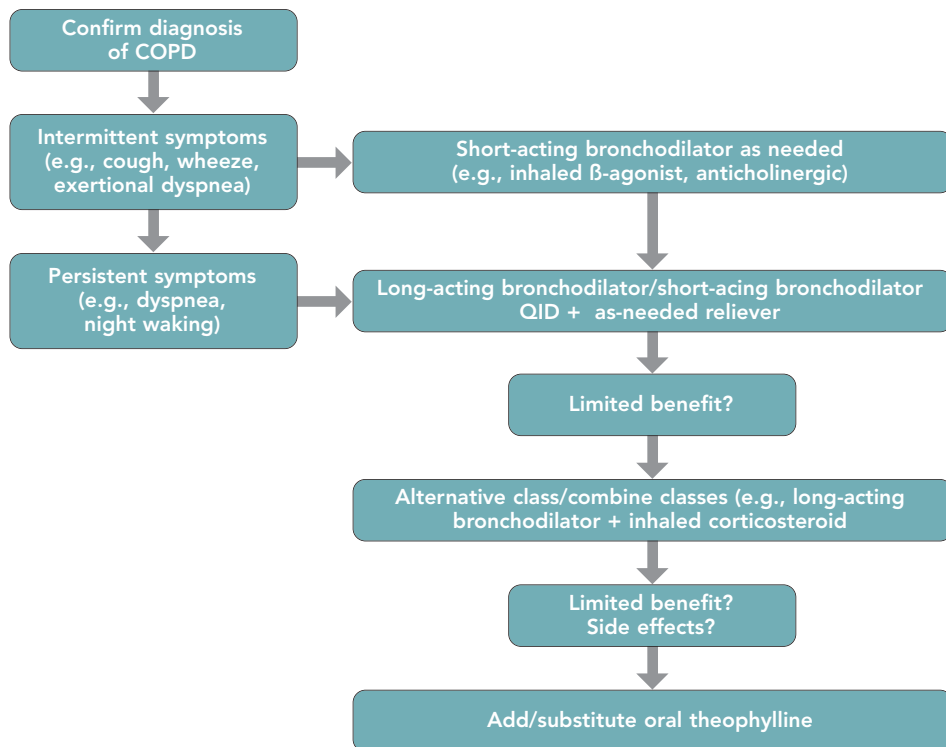
algorithm (see Exhibit 2).<sup>2</sup>

In contrast to the GOLD and ATS/ERS recommendations, guidelines published in 1999 by the VAHCS recommend one or the combination of two short-acting bronchodilators (specifically a  $\beta_2$  agonist and short-acting anticholinergic agent) as

**Exhibit 1: Recommendations for Each Stage of COPD According to the GOLD Guidelines.<sup>1</sup>**

	0: At risk	I: Mild	II: Moderate	III: Severe	IV: Very Severe
<b>Characteristics</b>	<ul style="list-style-type: none"> <li>Chronic symptoms</li> <li>Exposure to risk factors</li> <li>Normal spirometry</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub>/FVC &lt;70%</li> <li>FEV<sub>1</sub> ≥80%</li> <li>With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub>/FVC &lt;70%</li> <li>50% ≤ FEV<sub>1</sub> &lt;80%</li> <li>With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub>/FVC &lt;70%</li> <li>30% ≤ FEV<sub>1</sub> &lt;50%</li> <li>With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub>/FVC &lt;70%</li> <li>FEV<sub>1</sub> &lt;30% or ≤ FEV<sub>1</sub> &lt;50%</li> <li>Predicted, plus chronic respiratory failure</li> </ul>
Avoidance of risk factor(s); influenza vaccination					
Add short-acting bronchodilators when needed					
Add regular Rx with ≥1 long-acting bronchodilator; add rehabilitation					
Add inhaled corticosteroid if repeated exacerbations					
Add long-term O <sub>2</sub> if chronic respiratory failure Consider surgery					

**Exhibit 2: American Thoracic Society/European Respiratory Society Algorithm for Pharmacotherapy of COPD.<sup>2</sup>**

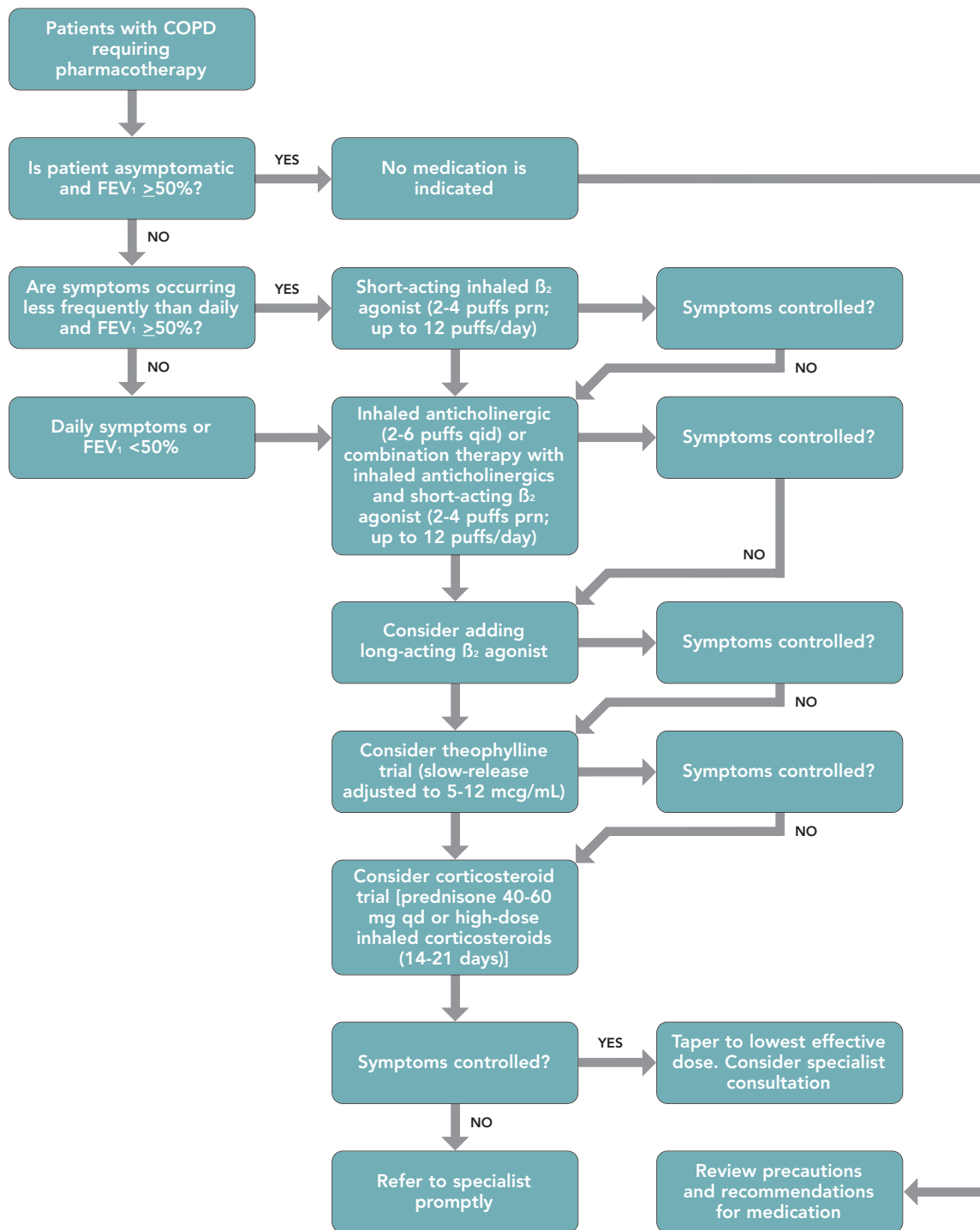


first-line therapy in patients in the primary care setting with persistent (daily) symptoms or FEV<sub>1</sub> <50 percent (Exhibit 3).<sup>3</sup> In clinical practice, combining these two types of agents is common. However, the clinical efficacy of this practice remains unproven.<sup>4</sup> The clinical efficacy of the combination of long-

acting bronchodilators, aside from additive effects on bronchodilation, also is unproven.<sup>5</sup>

Current evidence suggests that the use of one or two long-acting bronchodilators acting synergistically via different mechanisms may be the most effective strategy for treatment of stage 3 to 4 patients.

**Exhibit 3: Department of Veterans Affairs Guidelines for the Treatment of COPD in the Primary Care Setting.<sup>3</sup>**



Although long-acting,  $\beta$ -adrenergic bronchodilators are now readily available in most VA pharmacies, the use of the long-acting anticholinergic agent tiotropium is restricted. However, tiotropium (given once daily) has been shown to be superior to the short-acting anticholinergic, ipratropium (given four times daily), not only in terms of greater and more prolonged bronchodilation, but also with respect to patient-centered outcomes, such as dyspnea, need-for-rescue use of a short-acting inhaled  $\beta$ -agonist, health-related quality of life, exacerbations, and hospitalizations. Moreover, there is some evidence that tiotropium offers advantages over long-acting inhaled  $\beta$ -agonists. One large trial demonstrated that tiotropium is more effective at bronchodilation than salmeterol.<sup>6</sup> It also has been suggested that tiotropium may offer advantages over salmeterol in terms of symptoms and exacerbations. However the evidence for this is not definitive.

Another trial suggested that the combination of tiotropium and formoterol provides better bronchodilation than either agent alone.<sup>5</sup> Although it appears that this combination offers a clinical benefit, the evidence is not yet robust.

As outlined in an earlier article in this supplement, there is evidence that tiotropium significantly reduces the percentage of patients experiencing exacerbations and results in a non-significant trend toward a reduction in the frequency of hospitalizations for COPD,<sup>7</sup> a claim which cannot be made for other long-acting bronchodilators.<sup>8</sup>

Current VA guidelines for the use of tiotropium exclude patients for whom the medication would be beneficial. Of concern, to qualify for tiotropium patients must meet multiple criteria including

1. Ipratropium failure
2. Morning FEV<sub>1</sub> <50 percent
3. Two or more exacerbations requiring emergent medical care or one or more exacerbations requiring hospitalization in the previous year.

The evidence presented above indicates that VA guidelines should be liberalized to allow the general use of tiotropium for all individuals with COPD. At the very least, exacerbation-prone patients with FEV<sub>1</sub> >50 percent and very dyspneic but non-exacerbation-prone patients with FEV<sub>1</sub> <50 percent should be treated with tiotropium without having to meet current VA criteria. VA guidelines presently are under review and it is hoped that they will be amended to more closely reflect other national recommendations.

### Conclusions

Large-scale pharmacoeconomic studies are needed to fully investigate the cost effectiveness of using long-acting inhaled bronchodilators as first-line

therapy in patients with recurring symptoms and exacerbations associated with COPD. However, until this information is available, based on available evidence and professional society guidelines, we recommend that careful consideration be given to the multiple unique benefits of tiotropium along with the use of other long-acting bronchodilators as first-line therapy in patients with COPD in patients meeting VA usage criteria. **JMCM**

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**INSTRUCTIONS**

1. Read the supplement first.
2. Next, read the questions and mark your answers on the provided answer sheet (or make a copy). All questions and answers are based on the information in this supplement. Each question has only one correct answer.
3. After completing test and the activity evaluation, you may fax the answer sheet and evaluation to 804-747-5316, or mail to NAMCP CME Office, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.
4. You should receive your CME certificate within one month of completion. If you do not receive it, please call 804-527-1905 and ask for Ann Patrick or Katie Eads.

**1. Which of the following statements is false?**

- a. COPD is characterized by airflow limitation
- b. Airflow limitation is associated with an abnormal inflammatory response of the lungs to noxious particles or gases
- c. Airflow limitation is always fully reversible
- d. The inflammatory process associated with COPD involves neutrophils, CD8 cytotoxic lymphocytes, and macrophages

**2. Which system(s) is/are responsible for bronchodilation?**

- a. Sympathetic (adrenergic) nervous system
- b. Parasympathetic (cholinergic) nervous system
- c. Non-adrenergic non-cholinergic nervous system
- d. a and c

**3. Which of the following statements is true?**

- a. Investigation of the afferent and efferent pathways of cholinergic innervation found evidence of dysfunction along any part of the pathway, including muscarinic receptor function or transmission along the vagus nerve.
- b. It should not be assumed that responsiveness to anticholinergic agents in patients with COPD indicates that activity in parasympathetic nerves is increased.
- c. The role of the non-adrenergic, non-cholinergic nervous system in maintaining normal airway tone and its function in COPD is clearly understood.
- d. None of the above

**4. Which of the following statements is false?**

- a. Long-acting bronchodilators, such as salmeterol and formoterol, are effective in improving lung function in COPD.
- b. The short-acting bronchodilators have been shown to relieve dyspnea and improve exercise tolerance to a greater extent than long-acting bronchodilators.
- c. Theophylline is a weak bronchodilator that may have immunomodulatory, anti-inflammatory, and bronchoprotective effects.
- d. The common side effects of  $\beta$  agonists are cough and throat irritation.

**5. The primary mechanism of action of anticholinergic bronchodilators is:**

- a. By antagonizing the actions of acetylcholine, anticholinergic bronchodilators produce relaxation of airway smooth muscle
- b. Inhibition phosphodiesterase and adenosine leading to bronchodilation
- c. Binding to adrenergic receptors to stimulate bronchodilation
- d. None of the above

**6. Which of the following is not typically found in the COPD patient?**

- a. Pulmonary hyperinflation
- b. Increased residual volume
- c. Reduced inspiratory capacity
- d. Increased exercise tolerance

**7. Which of the following is not indicative of an exacerbation in a COPD patient?**

- a. An increase in dyspnea
- b. An increase in sputum volume
- c. An increase in sputum clearance
- d. Symptoms lasting more than a month

**8. Which of the following statements is true?**

- a. Ipratropium is more effective than tiotropium and salmeterol.
- b. Tiotropium is more effective than ipratropium and salmeterol.
- c. In patients with stage 2 to stage 4 COPD whose symptoms are not adequately controlled with short-acting bronchodilators, adding regular treatment with a long-acting bronchodilator does not appear beneficial.

**9. Which of the following is not a major barrier to compliance with COPD-inhaled medications?**

- a. Inability to stop smoking
- b. Lack of widespread access to appropriate diagnosis
- c. Lack of an oral agent
- d. Lack of widespread access to effective agents

## ANSWER SHEET

There is only one correct answer per question.  
Circle your answer clearly.

1. a    b    c    d
2. a    b    c    d
3. a    b    c    d
4. a    b    c    d

5. a    b    c    d
6. a    b    c    d
7. a    b    c    d
8. a    b    c
9. a    b    c    d

## ACTIVITY EVALUATION

1. What is your overall evaluation of this supplement?

- Poor     Fair     Good     Very Good     Excellent

2. Please rate on a scale of 1 to 5 (where 1 is poorly and 5 is extremely well) how well each of the following learning objectives was met:

Describe historical perspective on the approach to managing COPD

- 1    2    3    4    5

Understand the importance of cholinergic activity in COPD

- 1    2    3    4    5

Understand the pharmacology of long-acting bronchodilators

- 1    2    3    4    5

Describe the effects of treatment on quality of life and exercise in COPD

- 1    2    3    4    5

Describe the impact of acute exacerbations on COPD

- 1    2    3    4    5

Discuss the pharmacoeconomic burden of COPD

- 1    2    3    4    5

3. How relevant was this information to your practice?

- Not relevant     Somewhat relevant     Relevant

4. Do you feel that the material presented was balanced and fair?

- Yes     No

5. As a result of reading this supplement, please identify one or more concrete, measurable changes you would like to implement in your practice. This information will enable us to review specific examples of the effectiveness of this activity:

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6. Please indicate how much time you spent on this educational activity:

This information will be used to award your CME credit up to the maximum hours.

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Mailing Address: \_\_\_\_\_

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