

Welcome to the continuing education activity, **“Guideline-Based Approaches to Minimize the Progression of COPD: Improving Patient Quality of Life in Long-Term Care.”**

This activity is jointly sponsored by the American Academy of CME, Inc and Princeton CME, and is supported by an educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

This webcast activity is comprised of a case study presentation by Dr. Mark A. Stratton, Professor of Pharmacy and Langsam Endowed Chair in Geriatric Pharmacy and Director of the Institute for Geriatric Pharmacy at the University of Oklahoma College of Pharmacy in Oklahoma City, Oklahoma; and a main presentation by Dr. James F. Donohue, Professor of Medicine and Chief of the Division of Pulmonary and Critical Care Medicine at the University of North Carolina at Chapel Hill School of Medicine in Chapel Hill, North Carolina.

Please note that all faculty disclosures are listed on the introduction page of this activity.

To be eligible for documentation of credit, individuals must participate in the full educational activity, complete the 10-question post-test with a score of 70% or better, and complete the evaluation form accessible via the post-test link.

Participants who successfully complete the post-test and evaluation form online may immediately print their documentation of credit.

Dr. Stratton will now present the case study.

—
Our case today is MS. He is a 74-year-old male who has been at Shady Lakes Nursing Home for about the past 4 months. He is there because care for him at home became unmanageable due to the progression of his chronic obstructive pulmonary disease. It should be noted that he is on continuous supplemental oxygen delivered via nasal cannula at 2 L/minute, which has been required for the last several years. About 2 weeks ago, MS was hospitalized because of an exacerbation of his COPD, thought due to an upper respiratory tract infection. He was in the hospital for about 5 days and released back to the nursing home with new treatment considerations.

His patient profile included a smoking history of about 2 packs per day for about 35 years. He quit a few years ago. He also has had moderate alcohol intake. His medical history includes chronic obstructive lung disease, right heart failure, hypertension, polycythemia, osteoarthritis and diabetes mellitus.

And medications prior to his hospitalization included tiotropium 1 capsule via inhaler once per day, albuterol inhaler as needed for shortness of breath, furosemide 40 mg per day, potassium chloride 20 mEq per day, metformin 500 mg twice per day, lisinopril 10 mg per day, and ibuprofen 400 mg every 6 to 8 hours as needed for his arthritis pain.

Additional medications upon discharge from the hospital and readmittance to the nursing home included a prednisone taper over the next 2 to 3 weeks depending upon his COPD symptoms, the addition of the fluticasone salmeterol inhaler, the 250 µg/50 µg strength, 1 inhalation twice per day, and levofloxacin 500 mg daily to complete a 10-day course for the treatment of his upper respiratory tract infection.

Diagnostic and physical exam findings prior to hospitalization included arterial blood gases on room air of a PaO₂ of 54 mm Hg, a PaCO₂ of 55 mm Hg of mercury, a pH of 7.34, and an oxygen saturation of 85%. Note that he is markedly hypoxemic and hypercarbic and that he has a compensated respiratory acidosis. His sodium is 135 mEq per liter, his potassium is 3.8 mEq per liter, and his bicarb or carbon dioxide is 35 mEq per liter with a chloride of 97 mEq per liter. As you can see from his hemoglobin and his hematocrit of 17.8 g/dL and 54%, respectively, he is polycythemic. He had a white cell count of 7,600. His EKG revealed a tachycardia.

His pulmonary function test, prehospitalization, included an FEV₁ of less than 50% of predicted, an FEV₁/FVC ratio of less than 70%, indicative of stage 3 disease, and postbronchodilator showed no significant improvement in FEV₁.

His vital signs on readmission to the nursing home included a temperature of 97° F, a blood pressure of 128/76, and a pulse of 110 beats per minute.

Questions for consideration as you listen to Dr. Donohue's presentation include: What goals would be desirable to achieve for this patient's new therapeutic regimen? What are practices that caregivers should initiate to make sure that outcomes from therapy are maximized? What parameters should be monitored to assess efficacy and toxicity of therapy? And, finally, what parameters should be monitored to assess if an exacerbation of his COPD is imminent, and what should be done to intervene to potentially prevent worsening or possibly another hospitalization?

—
Thank you, Dr. Stratton.

COPD refers to chronic bronchitis, emphysema, or a combination of the 2. It's important to remember that COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to disease severity in individual patients. The pulmonary component is characterized by airflow limitation that is not fully reversible. Airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gasses. This is the definition from the Global Initiative for Chronic Obstructive Lung Disease. What's new here, just in general, is the emphasis now on extrapulmonary effects and the fact that it's an inflammatory disease. This is a change from the definitions that were used just a few years ago.

COPD is the leading cause of death and disability. The prevalence in the United States is 5.9% of the adult population. Over 10 million adults have already been diagnosed with COPD and 14 million are undiagnosed. It's the fourth leading cause of death in the United States and, surprisingly, as of 2000, the mortality in women has surpassed men. Older patients, particularly in long-term care facilities, commonly present with more severe disease, often requiring admission to a long-term care facility for continued oxygen and nebulizer treatments.

These factors have contributed to the ranking of COPD as a leading cause of burden in developing countries, and this is data from the World Health Organization in 2002. COPD ranks in sixth place when we look at the total disability adjusted life-years, which is a measure of the burden of a disease. And the thing to note is that COPD is increasing, and by 2020 will move much further up the list to maybe third place.

Next, we look at some data from Dr. David Mannino in *Morbidity Mortality Weekly Report*, and we see in the United States the mortality rates per 100,000 individuals. Around the year 2000, we see that women have caught up to men as far as COPD mortality; and in fact, of the 120,000 Americans that died, 61,000 were women, and about 59,000 were males. Prevalence in some of the studies that are still being reported will have a male predominance, but the male smokers are dying out and are being replaced by female sufferers of this disease.

What is very important for the long-term care facility is that, with COPD, there are frequently comorbidities, especially in older patients. These patients with COPD are at an increased risk for myocardial infarction, angina, and osteoporosis because of their inactivity, their smoking, and sometimes because of therapy. They get a lot of infections, including acute exacerbations of bronchitis and pneumonia. Many are depressed because of their loss of function. Depression may also have a physiologic cause in patients with COPD. Mediators that are linked to inflammation in the lung are known to lead to depression. Diabetes is very common in this population, as well as lung cancer. In fact, if you look at COPD mortality, one-third of the patients die of lung cancer.

More than 50% of the deaths in COPD are caused by non-respiratory diseases. Hospital discharges listing COPD as either a primary or secondary diagnosis are more likely to have a comorbid condition. In-

hospital mortality from congestive heart failure, hypertension, ischemic heart disease, and thoracic malignancies is also more likely in those with COPD than in those without. Smoking and the underlying pathology of systemic inflammatory disease contribute to the link to cardiovascular disease. This is an extremely important concept. In fact, many of the recent studies in our field have looked at the impact of different therapies for COPD on cardiovascular risk, and that is still ongoing.

Depression is quite common in COPD and there are certain chemokines that are released from the inflammation in the lung that may contribute, but also, psychologically, there is a lot of loss here of function, health, and well-being. The psychological diagnoses, especially depression, are common to COPD patients in long-term care facilities, and contribute to notable suicide rates in older adults. The depression has, along with the COPD, really a major effect on decreasing functional performance, lowering quality of life scores; it reduces adherence to medicines and delays timely care.

COPD is really a costly disease in the United States and many of these costs are actually in the more advanced stages of the disease. Here is the US cost in billions of dollars. We see \$18 billion for COPD direct costs, and \$14 billion in indirect costs, and the cost of asthma and hypertension pale in comparison.

COPD exacerbations are particularly prevalent in long-term care facilities and require extensive healthcare resources. Exacerbations comprise about 1% of all 11.7 million hospital admissions, and 2.4% of all 4.2 million acute medical admissions. The admissions due to COPD have increased 13% from 1998 to 2003. The length of stay, particularly if patients are admitted to the ICU and wind up in long-term care facilities, is often quite long—up to 10 days. The median for about 1000 patients in 200 practices is 2 exacerbations per year, and we will come back to that in a moment and show that as a function of the severity of the disease.

Next, let's explore the risk factors for COPD and the diagnosis for these patients.

Certainly there are genetic factors, like α -1 antitrypsin deficiency. There's exposure to particles in tobacco smoke, occupational dust, the dusty trades, indoor air pollution from heating and cooking, and poorly ventilated dwellings. This is a huge problem in the emerging nations, the poorer nations of the world, and outdoor air pollution is another factor. Other things that have impacted risk of COPD, believe it or not, are maternal smoking and the weight of a baby in-utero. These are studies done many years ago in England. They have a huge impact on lung growth and development. There's oxidative stress from smoking, gender factors, and age-related problems. The normal aging process interacts with COPD causing more trouble in a 70-year-old than in a 60-year-old. And then there are infections, low social economic status, poor nutrition, and a low BMI, which is a very important factor that we will revisit.

This is the classic Fletcher-Peto race horse effect. What happens if you smoke and you're at risk? You can see the top curve is those who have never smoked, or are not susceptible to smoking. On the y-axis is FEV₁ or lung function, and we can see patients from age 25 to 75. And the occurrence of both death and disability can be seen.

So, if you have never smoked, you are not susceptible, there is no risk. The second blue line, though, shows those who smoke regularly and are susceptible. There is some debate as to how many there are. 15% of susceptible smokers was a previously reported estimate, but we now think that is about 27%. When you stop smoking at age 45, you can see that the slope of that decline slows down. Now, if you stop smoking at age 65, it is pretty late, but it still slows the rate down. So, any time you stop smoking, along that downward spiral, it really helps. If you are genetically susceptible to α -1 antitrypsin deficiency, that decline curve will be much faster. For a non-smoker, the normal rate of decline is about 20 mL per year. A cigarette smoker with COPD loses 60 mL. And, if you stop smoking with COPD, it falls to 30 mL. So, disease progression or interaction with disease, disease modification, can be seen with cessation of smoking.

Here is the proof of that last statement: the lung-health results. On the left-hand side we see lung function, and this is a 5 year study of over 6000 Americans. And there is smoking intervention plus

placebo. There's also smoking intervention plus ipratropium bromide, and no intervention. And you can see that if you stop smoking after the screening visit, which is shown in the top line of the graph, the smoking intervention, which was nicotine replacement and counseling, produces a nice little increase in lung function. And then you see that the use of a medication really didn't do much—there is no difference between placebo and ipratropium in changing the slope.

The next slide is very important, though. If you continue to smoke you lose 60 mL per year over 5 years. And, if you are a sustained quitter, you regain a little bit of function and then decline at 30 mL per year. So, smoking cessation is the most impactful intervention. It's better than bronchodilators.

What about the clinical suspicion and confirmation of COPD? A clinical diagnosis of COPD should be considered in any patient who has any combination of the following: dyspnea, chronic cough or sputum production, or a history of exposure to risk factors for this disease, such as smoking. And spirometry is the gold standard for making the diagnosis. That evaluation for COPD using spirometry usually takes place around age 50—earlier than that, spirometry may not have changed. Later than that, usually the patient's condition will have progressed significantly.

Spirometry should be performed after the administration of an adequate dose of a short-acting inhaled bronchodilator—that will cut down on variability and will help to differentiate patients with COPD from those with asthma. A postbronchodilator FEV₁/FVC ratio of less than 0.7 confirms the presence of airflow limitation that is not fully reversible. Where possible, values should be compared to age-related normal values to avoid over-diagnosis of COPD, especially in the elderly. And what that means is some people use a standard of people over the age of 70 of the FEV₁/FVC of less than 0.65, but again, that is somewhat debated. So, we do a postbronchodilator test, but we do not treat on the basis of response to albuterol—that would lead to under-treatment of a number of patients. You really give a therapeutic test of at least 1 month, but we do use spirometry with pre- and post-albuterol to make the diagnosis of COPD.

Now, we want to get into the goals of treatment for your patients in the long-term care facility.

The first clinical goal: make the disease better if we can, improve it. And one example of this disease modification would be to change the decline in FEV₁. As I mentioned earlier, the change in FEV₁ usually with a smoker is 60 mL per year, and with smoking cessation it falls to 30 mL. There have been many studies, and we'll mention some of the different other therapies, like inhaled steroids that attempt to change this, or antioxidants, and they have all pretty much failed. Although we keep looking for other interventions that modify the course of COPD, so far, only smoking cessation has proven to be effective.

There are several objectives of COPD management—we want to relieve symptoms, improve exercise tolerance, health status, prevent and treat exacerbations, and prevent and treat complications.

The survival of our patients is obviously very important—we want them to live longer, but we want them to live well, too. The BODE index, which was published by Dr. Bart Celli in the *New England Journal of Medicine* last year, looks at a composite score of 4 variables. B is for body-mass index, and identifies when a patient can get too thin. O is for obstruction in the FEV₁. D is for dyspnea on a 5-point Likert scale, ranging from no dyspnea with normal activities, to "I'm so short of breath I can't get out of bed." And then E is for the exercise capacity and the distance walked in 6 minutes. When you divide patients into 4 quartiles, we see a lot of variability between the probability of survival over 52 months.

On the second graph, in contrast, we see that when measuring FEV₁ alone, greater than 50, between 50 and 36, and less than 35—which represents the old ATS staging of stages 1, 2, and 3—do not discriminate as well as the composite. Using common sense, it's always better to examine a patient using a variety of measures.

Survival is one of the important outcomes, and it's being tested in some of the interventions that we'll discuss shortly.

Here are the GOLD guideline definitions of the 4 stages of COPD—mild, moderate, severe, and very severe. The lung function measurements at all 4 stages show an FEV₁/FVC ratio less than 70% of predicted. We try to minimize risk factors in all of these patients, such as avoiding smoking. We administer influenza vaccination every year to the patients at risk. For every stage we add short-acting bronchodilators, such as albuterol and ipratropium. Patients with any stage of COPD may have chronic cough and sputum production, along with chronic bronchitis. We add regular treatment with 1 or more long-acting bronchodilators as the patient's stage of COPD progresses from moderate to severe, to very severe. Sometimes we combine different classes of drugs, and we will review each of the available agents.

Rehabilitation can be extremely useful in any stage, and does not require a formal program—a patient can go through rehabilitation at home. The patients with chronic cough and sputum production often will complain of dyspnea on exertion. These are the patients we need to screen and diagnose in the appropriate stage. Inhaled corticosteroids are often added for patients with more severe disease, especially if they have repeated exacerbations which are very significant consequences of COPD. In the very severe group, stage 4—occasionally stage 3 in an older person—we add long-term oxygen, and, we may consider surgical options for a very small minority of patients who are hypoxemic. For example, a patient who presents with upper lobe emphysema and a very low exercise tolerance would warrant a special consideration. An even more severe group would include chronic respiratory failure with oxygen retention of less than 60, CO₂ retention, and cor pulmonale with right heart failure. Remember that cor pulmonale sometimes could be due to another coexistent condition such as sleep apnea.

We mentioned the pharmacologic options to treat COPD include short-acting and long-acting bronchodilators. We also have glucocorticosteroids and combinations. We have vaccines for influenza, and antibiotics which primarily are used for acute exacerbation only since, in general, regular use of antibiotics is not encouraged and not indicated. Mucolytics have not been proven to be effective in the treatment of COPD, even though a lot of our patients have thick tenacious mucous. And then there is the nonpharmacologic treatment or rehabilitation for all patients—walking, breathing treatments, breathing exercises, oxygen therapy for the appropriate candidate, and surgery for a very rare candidate who would not commonly present in a long-term care facility.

Now, what about bronchodilators? According to the GOLD guidelines, bronchodilators are central to the symptomatic management of COPD. Short-acting bronchodilators are given on an as-needed basis. Longer-acting agents are given on a regular basis to prevent or reduce symptoms, and this is Evidence A. The principle treatments are β -agonists—both short-acting and long-acting; anticholinergics—both short-acting and long-acting; theophylline, and a combination of these drugs. In the West, we use theophylline less commonly in the geriatric population due to the numerous drug interactions and drug toxicities. Long-acting inhaled bronchodilators are more convenient than short-acting, and that's Evidence A. Combinations of bronchodilators improve efficacy and reduce the risk of adverse effects versus increasing the dose of a single agent. This sound strategy supports combination therapy using ipratropium and albuterol, for example, rather than quadrupling the dose of either one of those agents alone.

This schema outlines the current bronchodilator options for COPD. Short-acting albuterol has an onset of action of 1 to 3 minutes, and a duration of action between 4 to 6 hours, with dosing as needed. And then we have the anticholinergics. The long-acting β -agonist salmeterol is not used in the acute setting—it has a slow onset of action of 20 to 30 minutes, but it lasts 12 hours or more. It is administered with 2 inhalations of a metered dose inhaler twice a day, or if it's a discus, it would be 1 puff twice a day. Formoterol is a long-acting agent, but has a fast onset of action of 1 to 3 minutes with a duration of 10 to 12 hours. The usual dose would be dependent on the type of device—a dry powder inhaler versus some of the newer devices. The anticholinergic tiotropium is a dry powder inhaler and it is dosed at 1 puff every 24 hours. Theophylline would be dosed based on the serum levels and we use this drug less frequently for COPD—we do not use the 10 to 20 mcg/dL dosing range anymore; in the older population, rather we use 8 to 12 mcg/dL in our dosing. The fixed combinations would be albuterol and ipratropium and fluticasone and salmeterol. The combination of budesonide and formoterol is approved for use in asthma, but not yet in COPD.

The anticholinergic ipratropium has a slow onset of action, again, 20 to 30 minutes, and the duration is 4 to 6 hours. It is given 2 to 3 puffs 4 times a day with a metered dose inhaler and the dosage in solution is 500 mcg dosed 4 times a day. The long-acting agent tiotropium is given 1 capsule daily and has a very slow onset of action, 1 to 2 hours, but it lasts 24 hours.

The rationale for use of bronchodilators in COPD is very important. The physiologic effect is bronchodilation or relaxation of airway smooth muscle, so it improves the FEV₁. But even more important is the process of dynamic hyperinflation in some COPD patients, when air gets trapped in the chest and can't escape during periods of activity that cause the respiratory rate to increase. The lungs get bigger and bigger, but their function is very limited due to dyspnea. So, the symptom of shortness of breath, dyspnea, correlates more with air trapping and dynamic hyperinflation than the FEV₁. There are other nonbronchodilator effects on mucociliary clearance. There are some renal effects and some stimulatory effects, particularly with long-acting β -agonists and theophylline. The clinical effects of these drugs are to decrease breathlessness by improving airway resistance and decreasing hyperinflation, improving exercise tolerance, improving sleep quality, improving quality of life, and, most importantly, decreasing the frequency of acute exacerbation. These are events that really cause treatment challenges.

Some patients in long-term care will have irreversible emphysema, as shown by the pre- and post-bronchodilator lung function measurements evaluated in the hospital. A study from Dennis O'Donnell examines all patients, and the subgroup of patients with moderate and severe COPD. The FEV₁ doesn't seem to change too much. But if we look at the residual volume and functional residual capacity in the more severe patients, we see that these indices of air trapping come down almost 500 mL, much more than in the patients with moderate COPD. Even when there is not a good improvement in FEV₁, the long-acting bronchodilator should still be given because there will be less air trapping and the patients will symptomatically feel a lot better with that reduction in the functional residual capacity.

Here's an example of the combination therapy with studies that we did many years ago looking at test day 1 and test day 85. The top curve is the combination, the middle curve is albuterol, and the bottom curve, initially on test day 1, is ipratropium. And you see on day 1 you get a very nice 30% increase in FEV₁ that lasts about 5 hours. On test day 85, there's a little bit of tolerance to the albuterol and the dotted line is not quite as good as it was on day 1. The ipratropium is still pretty good and the combination is pretty good. The trouble with this combination, as you can easily see here, is that hours 4, 5, and 6 are below what we consider a therapeutic line. Short-acting agents really have to be dosed way too much for our patients. Every time that line falls below 15%, the patient probably has breakthrough symptoms and that's not favorable.

Now, as shown on the next slide, a study from Vincken looked at the St. George's quality-of-life test for long-acting agents, and tiotropium was compared to placebo in the United States, and in Europe it was compared to ipratropium. This is very good test, it's well validated, and the decline with tiotropium is very good. Our patients start with a score of 45 at test day 0, and after a little over 1 year, you can see the top line, ipratropium, is really still at baseline. But if we look at the tiotropium line, it falls all the way down to 40. The difference between 44 and 40, a 4 point difference, is what is considered a minimal clinically important difference. There is a highly significant improvement of the benefit of a long-acting agent given once a day versus a short-acting agent given 4 times a day.

This next slide is showing salmeterol versus ipratropium similar to the tiotropium study. Now, we're looking at lung function change from baseline over 12 hours. The top curve shows a nice smooth improvement with the long-acting β -agonist salmeterol. The line in between the middle area is the short-acting anticholinergic ipratropium and we see a fall between hours 3, 4, and 5, and then the second dose comes in. So, there is a nice benefit of using long-acting bronchodilators of both the β -agonists and muscarinic antagonist classes in the field of COPD.

I published a study a few years ago using tiotropium and salmeterol in COPD, looking at lung function at day 1 and day 169. The top curve is for tiotropium and the bottom curve is salmeterol. The FEV₁ is pretty similar over the first few days. Please note if you look at the time from -1 to 0, which is considered the

trough value, the very top curve, tiotropium day 169, shows a very nice improvement with both agents, and it persists a little better with tiotropium at day 169. There's a slight advantage to tiotropium in this study over salmeterol dosed twice daily and this was replicated in other studies.

The next slide is the series of studies showing a nice effect of long-acting β -agonists on improving quality of life. It appears that any bronchodilator that is long-acting really does cut down on exacerbations by about 24% to 25%. The number needed to treat would be 4 patients to reduce 1 exacerbation per year, which is a very good health intervention.

Here's an example of combining the bronchodilator tiotropium, an anticholinergic, anti-muscarinic agent, plus the long-acting β -agonist formoterol. This is the series of curves showing tiotropium and tiotropium plus formoterol either once or twice daily. The point here being, that particularly in the more severe patients, when you add different classes of drugs, you always get a little extra benefit.

Many patients in long-term care facilities use nebulizers, and recently the FDA approved 2 new long-acting β -agonist inhalation solutions: one is formoterol fumarate and the second one is arformoterol tartrate, both given every 12 hours. Other nebulized solutions of short-acting agents like albuterol and ipratropium are also available.

Now, what are the benefits of nebulizers? There are numerous studies showing really no benefit of nebulizers over metered dose inhalers. However, there are certain patient populations that do benefit from nebulizers, including the nursing home long-term care patients. Patients are not required to hold a deep breath, which is more challenging for the older population. Nebulizers involve less coordination than metered dose inhalers, provide a gentler method of administration, and more of the agent reaches the airways because higher doses are used. Although the agent might reach the airways to achieve more rapid and effective bronchodilation, you may have more adverse effects too, so use of nebulizers is a double-edged sword. Nebulizers are currently reimbursed under Part B of Medicare, and are commonly used by the older patient population.

One of the most popular combinations available is the combination of a long-acting β -agonist plus an inhaled corticosteroid. This is the combination of salmeterol and fluticasone. The rule from the Food and Drug Administration is the combination has to be superior to monotherapy. The top line shows the combination of fluticasone and salmeterol. The next 2 monotherapy arms are fluticasone alone and salmeterol alone. The bottom is placebo, and placebo always looks good, that's what is called a survival effect—healthy survivors stay in the study, while many others wash out. Anyway, if you look at the endpoint analysis on the extreme right-hand side, there is a nice improvement with the combination of 27% versus 14% with fluticasone alone, 19% with salmeterol, and 6% with placebo. So, these agents offer a very nice combination which improves lung function and can help relieve dyspnea in certain patients.

Inhaled steroids in the treatment of COPD are somewhat controversial and, in COPD, the addition of regular treatment with inhaled steroids and bronchodilators is appropriate for symptomatic COPD patients with an FEV₁ less than 50% of predicted, stage 3 and also stage 4. Those who have repeated exacerbations also do well. An ICS combined with the LABA, as we just talked about, is more effective than the individual components alone. The dose-response relationships and the long-term safety of inhaled steroids in COPD are not known. Please note, in the United States, the FDA has never approved monotherapy with an inhaled corticosteroid for COPD, although they certainly have for asthma. So, in COPD, the inhaled steroid probably should be combined with the LABA. Chronic treatment with systemic glucocorticosteroids or oral prednisone should be avoided because of the unfavorable benefit-to-risk ratio, and that's also Evidence A. That is not to say you should not use those drugs in acute exacerbation, but not chronically because they have too many adverse effects.

Here is one of the controversies: Do inhaled steroids slow the decline in FEV₁? And the meta-analyses, one done by Highland, one done by Sutherland, show a change of only 5 mL and 7.7 mL, so not a real big effect on slowing the decline. You really should use inhaled steroids, as we mentioned, combined with the LABA.

The next slide, from Don Sin, is a meta-analysis, not a prospective study, that looked at follow up of 48 months of therapy and looked at survival. There seemed to be a signal that inhaled steroids versus placebo improved survival.

This led to the TORCH study on the next slide, based on all-cause mortality. That would be deaths due to anything—COPD, cancer, and heart disease. Here, the primary comparison of all-cause mortality was the combination of salmeterol and fluticasone 500 versus placebo, which didn't achieve statistical significance, although it came close. The long-acting β -agonist actually did quite well. Fluticasone alone had a slightly negative effect at the end of the study. Inhaled steroids do not, at least with monotherapy, have much of an effect, if any, on mortality.

The next frontier is what we call triple therapy, usually appropriate for patients in stage 3 and stage 4 with more severe disease. It would include a long-acting muscarinic antagonist like tiotropium, a long-acting β -agonist like salmeterol or formoterol, plus an inhaled corticosteroid. And the first study to come out is the Canadian Optimal Trial published by Sean Aaron in the *Annals of Internal Medicine* this year, which compared tiotropium plus salmeterol, and tiotropium plus fluticasone and salmeterol.

The study was powered on the probability of remaining exacerbation-free and, at the end of the day, there wasn't really any significant differences in exacerbation. While the triple combination, the top curve, did seem to prolong the time to first exacerbation, it was not statistically significant.

However, as shown on the next slide, the combination of the triple, in the bottom curve, and the combination of the LAMA plus LABA really did improve the St. George's respiratory questionnaire. So, there is an improvement in quality of life. The next slide really shows some nice benefit on lung function from the triple drug combination.

Normally, you start with 1 agent, let's say tiotropium or salmeterol or formoterol, then you add the other agents on and give them for a period of at least a month to see if the patients do well.

We talked about the GOLD guidelines. There's a second ERS/ATS algorithm which is very similar to the GOLD guidelines, published by Bart Celli, and it's outlined here.

What about the other treatment considerations with these medicines?

β -agonists have adverse effects including tremor, tachycardia, and arrhythmia. Sometimes, early on, there are changes in the serum potassium and changes in glucose, but not too much. Long-acting agents cannot be used as rescue medications; short-acting agents surely can. Adverse effects of anticholinergics include a really dry mouth and difficulty in micturition, really only in elderly gentlemen with prostatic hypertrophy. They rarely cause constipation. If the drug gets in the eye, they might have some blurred vision. These are anticholinergic effects—rare drowsiness and dizziness, but these drugs are very, very safe by and large.

Systemic corticosteroids are very tricky drugs to use and really should only be used in exacerbations because of their adverse effect profile: glaucoma, cataracts, diabetes, osteoporosis, and myopathy. So, they really are to be avoided, if at all possible. Theophylline really needs to be given with caution because of the comorbidities that are often present, such as liver disease, heart failure, pneumonia, as well as the drug interactions of theophylline with various macrolide antibiotics and other types of agents that are metabolized in the liver. These are tricky drugs to use.

Now let's discuss contraindications in agents for patients with COPD. We rarely use the antitussives, particularly those with narcotics, because we need the patient to cough to protect their airways. β -blockers—many of our patients have heart disease where β -blockers are life saving, so we use selective β -blockers in COPD, but in low doses. Narcotics can be a real problem with respiratory depression, and particularly in patients who have CO_2 retention. Vasodilators can make your oxygen worse; you don't

know. Antihistamines are drying agents and sedatives can depress respiratory drive, so, just be careful—those agents are not recommended.

The last thing we want to get into is exacerbations.

The definition is not just having a bad day—it's a change in patient symptoms beyond the daily variations, which is sufficient to cause a change in therapy, usually around 2 days. Causes of exacerbations can be infectious or noninfectious—such as air pollution. Many are caused by viral and bacterial infections in long-term care facilities and patients often need to be hospitalized due to these exacerbations. The therapy is usually increased use of bronchodilators, oral corticosteroids, oxygen, and antibiotics. Patients experiencing COPD exacerbations with clinical signs of airway infection, increased cough, and sputum purulence benefit from antibiotic treatment. If the exacerbation is really bad, and the CO₂ goes up, then noninvasive mechanical ventilation can be really, really very helpful.

The consequences of airflow limitation in COPD all lead to a deterioration in health status. And if you have exacerbations, there is a profound effect on worsening this vicious cycle with a more rapid decline in lung function and premature mortality.

You can look at the baseline FEV₁—mild, moderate, severe, and very severe, and the frequency of these bad exacerbations is a function of how bad your lung function is. The British Group in London showed that patients with lung function of less than 1.25 have 2 and a half exacerbations per year, while people with good lung function have hardly any exacerbations.

Also, exacerbations not only have a big effect on survival, they have a terrible effect on the patient's quality of life. And this is from that same group, showing if you have either 0 to 2 exacerbations versus frequent exacerbations, you have a much worse score in your total St. George's score, the symptoms, activities, and impact.

The management algorithm for COPD exacerbations initiates or optimizes bronchodilator therapy or adds a second drug of short-acting agents. If there is resolution, so be it, then you might alter the ambulatory management; but if there's no resolution, you have to add antibiotics and oral corticosteroids. And if the exacerbation worsens in the long-term care facility or the patient is not making any progress over the first few hours, you have to consider referring them to the hospital for more definitive treatment.

Regarding the use of more drugs to reduce these terrible exacerbations, the Canadian Optimal Trial shows the big benefit comes with just really the tiotropium arm. Adding second and third drugs really didn't do too much for reducing exacerbations, so we're looking for other strategies. Triple drugs can be given, as I mentioned, because they can improve quality of life and lung function, but it doesn't seem they reduce exacerbations. One drug reduces the number of exacerbations I mentioned earlier by 25%, and that's a very impactful intervention.

There are many important patient and healthcare resource considerations for patients in long-term care facilities. When patients are initially screened upon admission, look for risk factors for COPD and try to stage it. Try to classify the comorbidities and catalog the medications to make sure there are no drug interactions that can hurt the COPD. We also want to look at healthcare resource use and improve staff competencies through education on appropriate treatment interventions and immunization policies. A yearly flu shot has tremendous impact on COPD. We want to develop ongoing management strategies to decrease the cost of patient care. We are interested in our patient's quality of life.

So, in conclusion, the cost burden of COPD and associated healthcare resource utilization is steadily increasing, and, unfortunately, will do so for many years to come. Older patients at long-term care facilities with advanced stages of COPD require specialized care related to their lung function, related to their disease progression, exacerbations, and immunizations. Comorbidities are prevalent in this aging population and contribute to management considerations for COPD. We also want to individualize treatment regimens using a combination of bronchodilators and nonpharmacologic interventions, which are necessary to improve patient quality of life in the long-term care setting.

Thank you, this concludes my presentation.

We will now turn back to Dr. Stratton for a discussion of the case study presented at the beginning of this activity.

—
Thank you, Dr Donohue. Let's revisit our case. You will recall MS is a 74-year-old male with an exacerbation of his COPD due to an upper respiratory tract infection that resulted in hospitalization and a change in his treatment regimen. Remember, too, he has hypertension and diabetes.

So, our treatment plan will include the following: to continue his tiotropium daily, to continue the short-acting β -agonist albuterol as needed. And, with the delivery of this particular medication, maybe we should consider the use of a spacer device to improve delivery if the patient cannot coordinate inhalation with activation of the metered dose inhaler. Or, maybe it might be necessary to deliver the medication via nebulizer. Also, we want to continue the 24-hour-per-day oxygen as his baseline blood gases suggest that this may improve mortality and quality of life. Our goal is to increase his PaCO₂ to greater than 60, not to normal, but to greater than 60, and that is a very important consideration. This will also improve his polycythemia.

Also, we want to continue to treat his right heart failure with furosemide and supplemental potassium chloride if needed. We want to monitor for efficacy by looking at signs of peripheral edema and his weight and we also want to monitor for toxicity of therapy by looking at potassium, BUN/SrCr and weight to assess whether or not he is becoming dehydrated, and also monitor blood glucose.

Changes in our treatment plan include tapering of the oral prednisone at 5 mg increments every 2 to 3 days, depending upon his pulmonary symptoms. And again, that will dictate the rate and the amount at which we taper the prednisone. We want to monitor for worsening of his blood glucose and blood pressure on the prednisone. We're going to initiate inhaled corticosteroids with a long-acting β -agonist fluticasone/salmeterol, to improve the quality of his life and potentially decrease exacerbations and hospitalizations, and we would also like to assess his immunization status by administering influenza vaccine every year, and administer a pneumococcal vaccine at least once. Since he is over 65, he should only need 1 dose of the vaccine. It may also be valuable to think about adding theophylline to this regimen if, in fact, this pharmacotherapy does not lead to an improved quality of his life. Theophylline can be a difficult medication to use, but for the pharmacists in the audience, you have the pharmacokinetic background to monitor and use this drug safely in your older population.

Thank you for joining us for this activity.

Please remember, to be eligible for continuing education credit, participants must successfully complete the post-test and evaluation form accessible via the post-test link.

Participants who successfully complete the post-test and evaluation form online may immediately print their documentation of credit.

This concludes the webcast activity.