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ReachMD

www.reachmd.com
info@reachmd.com
(866) 423-7849

Unleash the Truth About COPD

Announcer:

You're listening to ReachMD. This Medical Industry Feature, titled "Unleash the Truth About COPD" is sponsored by AstraZeneca.

In this podcast, Dr Han will discuss data from several studies regarding COPD. The study design, details, results and important contextual information are all included in the transcript of this podcast. For access to the transcript with these additional details and references cited for this program, visit ReachMD.com/UnleashTheTruth.

Dr. Han:

Hi, and welcome to today's program: *Unleashing the Truth about COPD*. My name is MeiLan Han, and I'm a Professor of Pulmonary Medicine at the University of Michigan in Ann Arbor. The purpose of this presentation is for disease state education and is not meant to imply efficacy or safety of any AstraZeneca or competitor products. There are no continuing medical education credits associated with this activity.

The focus of the talk today is really going to be all about exacerbations. We're going to discuss exacerbations from the physician perspective, and I think some of the things that we as physicians really care about include things like long-term lung function decline, permanent impairment associated with exacerbations, so we're going to talk about that, but we also are going to talk about what it's like to have an exacerbation from a patient perspective. What is the impact on quality of life? What is it like to be a patient living with COPD who has exacerbations? Because I think the more, we as physicians understand the patient perspective, really the more aggressive we're going to be about trying to prevent these events, and that's really what the talk today is about.

So, when we think about trying to have a more proactive approach towards COPD exacerbations, there are a couple things we have to realize. The first is from a patient perspective. Patients don't report all of these events like we think they do. One of the things I always do when I see a patient in clinic is I always ask them, "Have you had a flare-up of breathing trouble since the last time I saw you?" because I know a lot of times either they are taking care of it at home—they may not call—or sometimes they are actually calling another provider and I may not know about it, so it's really important that we be able to track these, so I always ask when I see my patients if there's an event that happened that they didn't call me about.

The other things that we know, unfortunately exacerbations are associated with more permanent declines in lung function, even moderate exacerbations. **[Information from a post hoc analysis of the WISDOM study in 317 patients with severe to very severe COPD to characterize lung function before, during, and after a moderate COPD exacerbation.]** We know that severe exacerbations in particular are associated with high risk of death in the subsequent year, so that's something I'm always thinking about and always get concerned about. **[Information from trial described in more detail on page 6 as the Quebec study.]**

We also know that exacerbations can have sustained and irreversible impact on quality of life, so that's something else that we're going to be talking about today as well.

When I talk to patients about exacerbations, it's not just the exacerbation itself that is a concern and has impact on their ability just to live their lives. It's the fact that these are unanticipated. It's the fact that they don't know when the next one's going to occur. What if it happens when they're away from home? What if it happens when they're traveling? All of these kind of "what if" scenarios that go through a patient's mind really inhibit the way that they live, their ability to travel, to attend important events, family functions, or just worried about getting sick, or if they do get sick, how is that going to be managed.

One of the things that I think makes COPD tricky is that it is a very complex and heterogeneous condition. So we know patients differ in

terms of their symptoms, we know that they differ in terms of rates of lung function decline, in terms of the kinds of comorbidities they have, and then finally their risk for exacerbations, which actually can change even in the same patient over time, so this is why things like the GOLD recommendations currently take into account both symptoms, lung function and future risk for exacerbations, and that's something that I think we as physicians really have to kind of own when we're thinking about caring for these patients as well.

So, we know that from a public health perspective exacerbations are associated with very high morbidity and mortality.

COPD is currently the fourth leading cause of death in the United States and is responsible for over 1 million ED visits, close to 700,000 hospitalizations and 124,000 deaths annually in the US alone. **[Information from a surveillance report for COPD in the United States from national data systems for adults aged ≥ 25 years from 1999 to 2011. Numbers are approximately: 1.4 million ED visits, 676,000 hospitalizations, 124,000 deaths.]**

I don't know if you are like me, but when I hear figures like that, it's almost hard to even get your head around because they are so big, and all I can see are sort of my patients in my practice, but I think if you take each of those numbers and if you think about it as being a real patient and then you think about the doctor and the nurse and the MA and all the people that are required to care for that patient during that ED visit or during that hospitalization and the impact that that has on work loss and other aspects of society, the numbers truly are staggering. And I think it's a call to action, not just for us as healthcare physicians but really as a society that we need to pay more attention to respiratory health and to COPD and COPD exacerbations in general.

So, one of the things that you're going to hear me say a couple of times today during the presentation is that even 1 exacerbation is too many. So, from a patient perspective, even 1 moderate or severe exacerbation can actually lead to permanent declines in lung function, **[Information from the UPLIFT trial and the COPDGene study. The UPLIFT trial was a 4-year, randomized, double-blind, placebo-controlled, parallel group trial. A post hoc analysis of the UPLIFT trial was conducted to compare the rate of decline in lung function in patients with moderate to very severe COPD before and after a single exacerbation. The analysis compared the rate of decline in lung function before and after a single moderate (required use of antibiotics or systemic steroids) to severe (required hospitalization) exacerbation in patients who experienced only a single exacerbation during the trial. COPDGene is a multicenter, longitudinal, observational, cohort study that has enrolled current and former smokers. The study obtained spirometry and detailed respiratory illness history at the time of enrollment and captured exacerbations in longitudinal follow-up assessments. Exacerbations were defined as acute respiratory symptoms that required the use of either antibiotics or systemic steroids or by the need for hospitalization.]** and for severe exacerbations where the patients are hospitalized, we know that it's associated with increased risk for death. **[Information from trial described in more detail on page 6 as the Quebec study.]** That's really something... I think we hear about exacerbations all the time. Patients are calling in frequently and needing medications, and so we get I think a little bit callous because it's just something we hear about and deal with a lot, but for an individual patient, it could mark a really significant event in terms of change in their disease trajectory, and we're going to talk more about that during today's presentation. This is really, for me, why it's so important that we think about how we can prevent exacerbations.

So, when we think about the event, I know I have a tendency to think, "Well, the exacerbation is that 5 days or that 7 days when I gave the antibiotics or steroids," and then in my mind it's done because I've written the prescription, I've talked to the patient, and I can kind of check that box; but when we think about an exacerbation event from a patient perspective, there may have been 2 or 3 weeks of the patient not feeling well before they even picked up the phone, and it may be months, months, before they are feeling back to where they were, so we can talk about maybe knocking half a year off the calendar for a patient when they have an event in terms of how it's going to impact their lives, and I think that's something that we sometimes fail to appreciate.

So, the WISDOM study, while primarily was done to understand the impact of inhaled corticosteroid withdrawal, one of the interesting features of the study is that they actually incorporated mobile spirometry. **[Information from the WISDOM study. The WISDOM study was a multinational, randomized, double-blind, active-controlled, 12-month inhaled corticosteroid (ICS) withdrawal study in patients with severe-to-very severe COPD. Patients received triple therapy run-in (long-acting muscarinic antagonist and long-acting $\beta 2$ -agonist/ICS) for 6 weeks and were randomized to continue triple therapy or stepwise withdrawal of the ICS (dual bronchodilator group) over 12 weeks. The primary endpoint was the time to the first moderate or severe COPD exacerbation during the 12-month study period. Moderate exacerbations were defined as an increase of at least two lower respiratory tract symptoms related to COPD (shortness of breath, sputum production [volume], sputum purulence, cough, wheezing or chest tightness), or the new onset of two or more such symptoms, with at least one symptom lasting 3 or more days and for which antibiotics, systemic glucocorticoids or both were prescribed. A severe exacerbation was defined as an exacerbation requiring hospitalization.]** Unlike many trials where we had data, say, maybe only every 3 or 6 months or even sometimes only yearly, in this study they actually had data done at home on mobile spirometers. And what this allows us to do is to look at how lung function changed before an exacerbation, during the exacerbation and actually after the exacerbation.

One of the really interesting things is that even 3 weeks before the exacerbation event we start to see lung function go down. But unfortunately, over the next several weeks—and in this study they sort of examined the 8 weeks before and the 8 weeks after—the lung function really never recovered, at least during that 8-week post time frame. So, it's interesting that the prodrome may be going on for a while before the patient ever calls and notifies us that something is going on and at least in some cases on average never really quite got back to where they were before, and we certainly, I would say, hear that from a lot of patients, again this concept that recovery really can take a long time.

So, there's also some really interesting data coming out that has come out of COPDGene looking at lung function decline after exacerbations. So, you remember COPDGene is a large observational study. It's been going on for almost 10 years now. And they looked at lung function decline kind of across the board, across GOLD stages, between the baseline visit and their second visit, which happened at year 5, and they looked at whether the patient had had a severe exacerbation and then what happened to lung function decline in the subsequent 5 years. The most rapid decline was actually witnessed among GOLD 1 subjects. **[Information from a follow-up analysis of the observational COPDGene study on the first 2000 patients who returned for a second visit 5 years after enrollment.]**

So I think a lot of times we think, "Well, I only really have to worry about these severe events in my really sick patients because they might end up on the ventilator," and that's probably true, but again, it's really interesting that they—that in this particular study some of those longer-term effects, like declines in lung function, were most felt by the patients actually with GOLD 1 disease, so that really, I think, clues us into the fact that we need to be thinking about prevention, not just in our really severe patients but essentially in all of our patients.

There's another study here that looks at who's having exacerbations. **[Information from a retrospective observational cohort study using administrative claims and medical record data identified from the HealthCore Integrated Research Database. The HIRD is a large, diverse collection of medical and pharmacy claims data from geographically distributed health plan members (both commercial and Medicare Advantage) across all 50 US states. Patients from the screened medical record population with spirometry-defined COPD (FEV1/FVC ratio < 0.7) formed the confirmed COPD population and spirometry records were used to categorize patients by GOLD classification. Moderate exacerbations were defined as a pharmacy claim for an oral corticosteroid or antibiotic filled ≤ 7 days from an office visit with a diagnosis code of COPD or an ER visit with a primary diagnosis code of COPD.]** Again, I think sometimes we think, "Well, it's just my GOLD 3 patients," or "it's just my GOLD 4, my super sick patients that I really have to worry about," but what's interesting is that while it's probably true that on average our patients with the lowest lung function have the most events, in this particular study, when they looked at the number of events that were happening across the spectrum, actually the most just kind of absolute number of events was actually highest among the GOLD 2 group. So, again, I think this just really brings home and emphasizes that any patient can have an exacerbation and that they're really not good for all of our patients.

So, I'm always trying to do mental calculations for mortality risk and so I think many of us depend on BODE. Right? So that's one of the best mortality predictors that we have, which includes BMI, FEV1, dyspnea, and 6-minute walk, but I always sort of include this extra checkmark in my head when I'm thinking about risk, and that's: Did the patient have a severe exacerbation? We know there is some data from a study using some registry data from a health insurance group in Quebec, and for patients that had a first-ever hospitalization for COPD, roughly 50% of patients died within 3.6 years. Think about that. So, this is sort of another thing that I always think about when I'm thinking, "Do I need to be worried about this patient?" "How rapidly are they progressing?" "Is this a super high-risk patient?" Just that first severe exacerbation was associated with median death within 3.6 years, so this is another real red flag for us as clinicians. I would say, no matter what the GOLD stage, that this patient is at high risk for future events.

I think one of the most challenging things that we try to do as clinicians is try to predict which patients are going to have events.

I think trying to predict who's going to have an exacerbation is one of the most challenging things that we do. There is some good data that was published from the ECLIPSE cohort, which was an observational cohort, and this data that was published in the New England Journal took some of the baseline characteristics for these patients to try to identify who was at increased risk for having events in the next few years, and what they found is that perhaps one of the strongest predictors for a future event is simply having had 1 event in the past [year]. Once you've had 1, your risk for having a subsequent event goes up.

Other things, however, that they found were lower lung function at baseline and also patients who were more symptomatic using the SGRQ. **[Information from an analysis based on data collected as part of the ECLIPSE observational study, which recruited patients with moderate to very severe COPD (N=2138).]** Now, if you're like me, I don't do SGRQs outside of a clinical trial, but what I do, do in clinic, is the CAT because it's much shorter, and there is evidence from other studies that the CAT actually can be helpful in also helping us with risk prediction for which patients are going to have future exacerbations.

So, these are the kinds of things that I talk to my patients about in clinic. I get their prior exacerbation history. "What's happened since the last time I saw you?" I get lung function, and I try to assess CAT. These are the things that I'm doing and the calculations I'm going

through when I kind of think about is the medication regimen that a patient is on adequate or do we need to think about intense medication.

That same Quebec study that I mentioned also looked at what happened with not just the first event but when was the second event and when was the third event, and what they found was that the median time between successive severe exacerbations decreases with every new severe exacerbation, so in other words, the time course starts getting shorter and shorter and shorter. Once they have an event, then that makes hospitalization come faster and the next hospitalization comes faster. I can definitely say that in my experience I've seen that in my practice where you have a patient that for whatever reason had been doing very well, and then all of a sudden they have that hospitalization, and then you cannot keep them out of the hospital. It's like a flip has been switched, and it can be very, very difficult to get patients out of that spiral. Some patients ultimately do pull out. And I have to be honest. I'm never 100% sure what we've done. Obviously, we intensify treatment. Obviously, they're going to get more antibiotics and steroids. This is, I think, an area of medicine where I really would like to understand it better, what kind of triggers some of these spirals for patients, but I think the bottom line is that the risk for rehospitalization for COPD goes up with every subsequent severe event, so these are the patients we really have to worry about.

One of the other tricky things about this is that patients—not only do they underreport but they delay reporting, so I think this is where the onus is on us at every visit to take the opportunity to educate our patients about when to call and why to call, what an exacerbation is, how we can help them and when they need to call.

In one particular survey of COPD patients, over 40% did not take immediate action; they kind of waited. **[Information from a global patient survey was completed by 2000 patients with COPD, chronic bronchitis, or emphysema to gain insight into patient perceptions of COPD and exacerbations. Patients in the United States were not included in the survey. A symptom-based definition of exacerbations was used (a worsening of at least 1 symptom of COPD lasting for at least 48 hours).]** And I get that. I think patients don't want to bother us. They may also be somewhat in denial about the fact that they are actually having an event and so they delay calling, but unfortunately, I think sometimes the delay in calls may actually make it so that we don't get on top of things fast enough and then ultimately can lead to worse outcomes, so having a COPD exacerbation action plan for each of your patients I think really makes a lot of sense. And I think every visit is really an opportunity when we talk to our patients to really re-educate them about this sort of important aspect of the disease and when to call.

So, I want to spend a few minutes talking about health and life burdens of exacerbations.

I've sort of alluded to this. But when we talk to patients about exacerbations, it's not just, "Oh, I'm feeling short of breath." These events are paralyzing for patients. All of a sudden, they can't walk to the mailbox; they can't take a shower; they can't get dressed in the morning. Suddenly their lives are not livable.

In one particular study they reported that at even a year after moderate exacerbation patients reported a roughly 10% greater increase in dyspnea. We also can see up to or even more than 50 meters lost in a 6-minute walk distance after a moderate exacerbation. **[Information from data were acquired through a prospective observational study in a Veterans Affairs medical center to evaluate the immediate and subsequent impact of moderate exacerbations on the BODE index and its components, and the value of the change in the BODE index to help predict subsequent outcomes. A moderate exacerbation was defined as an event characterized by a sustained worsening of respiratory symptoms for at least 2 days, requiring: a visit to a doctor or the emergency department, treatment with antibiotics or systemic steroids or both, not necessitating a hospitalization. Pulmonary function tests and the 6MWT were performed following American Thoracic Society's guidelines. Dyspnea was assessed using the MMRC dyspnea scale.]** This is why normally, say after a patient has had a hospitalized exacerbation, it's really important recent data suggests we need to get those patients within the first 90 days to pulmonary rehabilitation.

Normally, pulmonary rehabilitation is a huge piece of my treatment for patients. Even before exacerbations you want to have those patients really in the best exercise fitness level as possible. And so just this kind of prolonged dyspnea, the prolonged exercise impairment that we can sometimes see I think points to the fact that we as physicians need to be even more proactive with our patients, both about treating events and then making sure they're getting appropriate therapy like pulmonary rehab to the extent that they can afterwards.

It's interesting when you talk to patients, patients with COPD describe the impairments that they have with exercise differently than other kinds of patients. They may say things like they can't get enough air in, that their breaths are really shallow. I think that some of the different descriptors that we see out of patients really relate to the hyperinflation that we see with emphysema that's really, I think, unique to COPD. And that impact of hyperinflation on not just ability to breathe but the dynamic hyperinflation that we can see with exercise really impacts our COPD patients.

I have had multiple discussions with patients over the last few weeks, and I have said to them, “Your prescription for the next few weeks is to get outside. You have my permission. I want you to get outside. I want you to walk. You have got to kind of, to at least some certain extent, start to resume some of your normal activities.” Because in some cases I think the anxiety and depression that are associated with the disease and is compounded by exacerbations may be even worse for some patients than some of the breathlessness associated with the disease itself.

The other thing that can happen with exacerbations is it's not just the lungs. So, the rest of the body can also be impacted by COPD. We don't clearly understand all of the reasons why. I think, I suspect it's because COPD exacerbations are diseases of inflammation. We know there's increased inflammation. We know white blood cell count is up. And so, what we can also see with other aspects of the body, there's over 2-fold increase risk of myocardial infarctions associated within the 5 days around exacerbation. We also can see up to a 40% increase in strokes within 10 days. **[Information from a case-series study conducted in 25,857 patients with COPD to assess the magnitude and timing of the risk of MI and stroke following a moderate COPD exacerbation from those entered in The Health Improvement Network (THIN) database in England and Wales over a 2-year period.]** So, this means that these are all things that we have to be thinking about when we're treating patients for exacerbations. We have to be on alert if symptoms, for instance, aren't getting better, and this can be really challenging for us as pulmonologists trying to figure out is it the heart? Is it the lungs? What's going on? Why isn't the patient responding to treatment? So, it's really something I think we all have to be thinking about is, “Well, maybe I'm treating the exacerbation, but perhaps something else—something else is going on.” In fact, I can think about one patient in my own practice within the last couple of weeks. It's been back and forth between me and the cardiologist. I said, “I've done everything I can do,” and so we've been trying to adjust some of the cardiac medications as well. So, this is, I think, one of the challenges that we have with COPD. It's very much a systemic disease.

So, when we're thinking about how can we prevent these events, how can we optimize management for our patients, first we think about risk, and then we think, “Okay, what can I...” “If I think they are at risk, what can I do to optimize their care?” So, clearly, pharmacotherapy, making sure they're on adequate preventative medications is important, but other things to think about include smoking cessation.

We also need to make sure that patients are vaccinated. This includes influenza and pneumococcal vaccines. And then clearly for patients with more advanced disease, we do have some other options like things like lung volume reduction surgery in the case of transplant. We also have endobronchial valves that have been approved as therapies for patients with advanced disease.

Pulmonary rehabilitation can have great effects on exercise capacity, dyspnea, quality of life, depression, anxiety. Rehab can impact all these. I realize that it's maybe challenging. But trying to get patients both socially engaged with other patients but also get that exercise that they clearly need is also really, I think, important when we're thinking about global management for patients. And then clearly for some patients there's going to be other more advanced therapies that may be required, things like, for instance, lung volume reduction surgery or now the endobronchial valves that have been approved. But again, I think it's really important to think about our patients holistically and think about them across the spectrum. What can I do, first from a pharmacotherapeutic standpoint, but also from a more global standpoint.

So, we've talked about the fact that patients, unfortunately, don't report; they underreport. **[Information from a multinational study, patients were interviewed in the following countries: France, Germany, Spain, Sweden, and the United Kingdom.]** And we've talked about the fact that **[moderate or severe]** exacerbations can be associated with declines in lung function, severe events can be associated with increased risk for death, and that exacerbations can have, unfortunately, sustained impact on quality of life, and yet at least in one survey when we asked patients, less than 2% of patients could actually explain an exacerbation. And I think it's a little bit unfortunate because even the word exacerbation a lot of my patients have a hard time getting out, much less try to explain what it is, so a lot of times I'll use the word flare-up with my patients and try to use that word again and again to kind of reiterate another way of thinking about it. And up to 50% of patients actually do not even report their exacerbations, so again, I think that comes back to the education piece.

So, another thing that I wanted to touch on and I think is particularly relevant now is the patient/physician relationship. My patients really want to talk to me. They're talking to me about their breathing. They're talking to me about the fact that they're getting depressed because they can't go out. They're talking to me about how things are getting harder because they're not exercising the way they should. And so I'm really trying to use this opportunity for this kind of change in our practice paradigm right now to really listen to my patients and to really hear what they're saying and encourage them to tell me about how they're doing so I can better help them.

AstraZeneca sponsored a **[market research]** survey to look at patient and physician perceptions around their care and around exacerbations, and the survey included both primary care physicians and pulmonologists, and it also included US patients diagnosed with COPD. **[Information from a market research survey. The market research involved 232 patients with COPD and 150 physicians**

(PCPs and pulmonologists.)

And they asked patients and physicians about gaps between symptoms and diagnosis, and interestingly, roughly a similar percentage of physicians and patients, roughly 60%, reported that they felt there was a significant gap between when symptoms started and when they were ultimately diagnosed with COPD. And interestingly, physicians thought that gap was even longer. And I was thinking about some of the patients that I've diagnosed recently, and I really try to go back and say, "When did you..." For instance, maybe, "When did you start smoking?" "When did you start having symptoms?" "When did you start having flare-ups like chronic bronchitis maybe before somebody even told you, you had COPD?" And I think this is true. I mean, you can kind of see the writing on the wall for many years before a patient actually receives a diagnosis of COPD.

And then the survey asked both physicians and patients what were some of the reasons that were driving those gaps, and a lot of the reasons were the same, but it is interesting to look at some of the differences in physician versus patient perception. More physicians felt patients were, perhaps, in denial about COPD or that perhaps the symptoms weren't severe enough to hit someone's attention or that there may have been a delay for patients getting in to see their physicians. Patients also, I think, admitted that symptoms weren't severe enough to be considered COPD, and I think this is where the education piece, not just in the office but honestly from a public health perspective, I really feel like we have not done a good enough job just, I think, for society to help people understand that, no, it's not normal even if you are a smoker to be short of breath, and yes, this is something that you should talk to your doctor about. So, I think again this kind of speaks to some of the gaps in education that we have.

When we see patients and get a diagnosis and we talk to them about all the things that we as physicians want to talk about, I think it is one of those moments where we're saying all of these things and the patients hear very, very little. So we probably talk about smoking and that this is going to be progressive and we need to control symptoms with medications, and we're talking about pulmonary rehabilitation and loss of lung function, and honestly, the patient just hears, "I was diagnosed with COPD, and of course I need to stop smoking, and I got some medication." So, I think this raises the point that we need to tell patients, and then we need to tell them again, and then we need to tell them again.

So it's really important, a lot of times I'll see patients back for, say, that second or third visit and I'll find out they stopped taking their medications because they didn't notice that it did anything, and that's where the education piece needs to come in and say, "I hope that this medication makes you feel better, but this is actually a preventative medication, kind of like your blood pressure medication, and we need to take this to help prevent something bad from happening, not just helping you to feel better today. I hope it makes you feel better today."

Every time the patient comes in, I always look at the prescriptions that they've got, and then I say, "Well, what are you really taking?" And it's never the same. That's where it gives us that opportunity again to remind patients and then kind of hit all of these highlights again. Again, "What is an exacerbation?" "When do you need to be calling me?" "Why do we take our medications?" What can we do as your disease progresses?" And this is where sort of that building that relationship with our patients, I think, becomes so incredibly important.

Announcer:

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For access to the video presentation, transcript, including the details of the COPD studies outlined by Dr. Han and references cited for this program, visit ReachMD.com/UnleashTheTruth. This is ReachMD. Be part of the knowledge.

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