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Specialty Provider Insights on Evolving Paradigms in COPD

Announcer:

Welcome to CME on ReachMD. This activity, titled "Specialty Provider Insights on Evolving Paradigms in COPD," is jointly provided by the Postgraduate Institute for Medicine and ASiM and is supported by an independent educational grant from GlaxoSmithKline. Recorded in New Orleans, this replay of a live broadcast features a panel of pulmonary experts who answered questions from the audience. Before beginning, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Now, here's Dr. James Donohue.

Dr. Donohue:

Good evening. I'm Dr. James Donohue at the University of North Carolina, and I welcome you to the meeting tonight. This is a live CME program on the evolving paradigms in COPD. Now, I was – I'm from the University of North Carolina where I was Chief of Pulmonary, and presently am a professor. And I'm one of the three presenters this evening. Joining me are Dr. MeiLan Han and Nicola Hanania. Welcome to you both. I'm sure we'll have a great program. Dr. Han and Hanania will be sharing their insights a bit later on. And before we get started, I have just a quick housekeeping note for our viewing audience. We encourage you to participate by submitting questions for our panel using either the Q&A box, as seen on your screen, or through Facebook or Twitter by using the #COPDbroadcast. First, I'm up with addressing the unmet needs of COPD patients, and a little background to understand the problem before I turn it over to my colleagues. Now, this is the definition of COPD, which I'm sure you've seen, but the important aspects are common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is either through the airway or alveolar abnormalities caused by significant exposure to noxious particles or gas. Now, I won't go through this whole slide, but there are a couple of points from the COPD etiology, pathobiology, and pathology from the GOLD guidelines. Etiology is exposure to smoking and air pollution, perhaps biomasses becoming extremely important, and a host of factors; for example, the most common one would perhaps be alpha 1 anti-trypsin deficiency, and the pathobiology involves impaired growth. And we'll talk a little bit about that; factors that happen in childhood, and we'll all make some comments. And then we'll have accelerated decline in lung function that's always been a target of our therapies to see if we can slow that decline. And then lung injury and then lung and systemic inflammation are very important. And in the pathology, of course, a big emphasis on the small airways and the abnormalities there, as well as emphysema and of course some of the systemic things leading to two important aspects that are highlighted in gold; airflow limitation and the clinical manifestations, the symptoms, exacerbations, and comorbidities are extremely important. Now one thing that we'll talk about is illustrated in this slide by Lange. It's very important. Not everybody, when lung growth is essentially completed, let's say at age 50 or 40, are the same or have the same natural history or FEV-1 progression over time. If you look at the top curve, that's the normal growth and normal nonsmoking curve. The second one would be smoking with a normal growth curve. But many people, because of either infection in childhood, low birth weight, maternal smoking in utero, parenteral smoking, childhood asthma; a whole host of factors that have recently come to the fore, they start out at about 60% of lung function. And the top curve shows that if they stay and don't smoke, they're alright. But if they smoke all for that lower lung function, they could be in for some early difficulties with their disease. So that – their genetic factors are important in influencing disease progression, age, and gender. And perhaps women are a little more disproportionately involved. Lung growth and development is very important. Exposures to particles,

either through cigarette smoking and biomass, social economic status, asthma and airway hyperreactivity, chronic bronchitis, and infection. All these go in. Now again looking at the pathology, pathogenesis, pathophysiology, again, chronic inflammation with structural changes. We all know in the pathogenesis, COPD is about oxidative stress, protease, anti-protease, imbalance, inflammatory cells and mediators. And as we look more and more at imaging, we see peribronchiolar changes in the airway and interstitial fibrosis. So these all lead to airflow limitation, gas trapping, gas exchange abnormalities, mucus hypersecretion, and maybe secondary pulmonary hypertension in some patients. Now we have many administrative devices. I'm not going through them all, but these are very important. They're important in the world to personalize medicine to target the device to the individual needs of our patients. So we have tried powder inhalers, many of which are shown here. We have one example of a nebulizer with MAGNAIR maybe for people in nursing homes, people with hand coordination issues, weakness, and frailty. We have some MDIs, and primarily DPIs. And you'll be hearing tonight, in this program rather, about some of these changes due to the various device. Now, from the GOLD guidelines, misuse of inhalers is very common in COPD. Down the left side, we have the metered dose inhalers and the percentage of patients making mistakes. And just look at the top, you see 27, 26, and 19. And on the dry powder inhaler side, again very important changes in errors. So failure to coordinate the MDI activation with your inhalation with the MDI, too short of breath hold, too rapid of inspiratory flow will give you turbulence, and inadequate shaking of the inhaler before the use. Abruptness continue of inspiration as the air impacts your throat. Or you activate the MDI when you're already up at total lung capacity, you're not going to get any. And the firing of the MDI multiples times, you see that into chambers. And the DPI, not holding the device correctly, holding some of these things upside down or on their side, exhaling through the mouthpiece, not exhaling down a residual; a whole host of difficulties. And from GOLD, a large proportion, maybe 49-76% of patients use their inhalers incorrectly. And the GOLD guidelines recommend rechecking inhaler technique at each patient visit, either yourself or someone in your staff that could help you do that; that's very important. Three key points from GOLD from the – about inhaler devices: The choice of the inhaler device has to be individually tailored. And it depends on the patient's access, cost factors, prescriber wishes, and most importantly the patient's ability and preference. Now, it's essential to provide instruction and to demonstrate proper inhalation technique when prescribing a device to ensure that inhaler technique is adequate, and recheck it at each visit. And then lastly, and this is very important, inhaler technique add adherence to therapy should be assessed before concluding that current therapy requires modification that you have to step up. And we see this all the time. Please, don't step up, don't do some surgical lung volume reduction procedure or something before actually making sure the patients are truly adhering. So, factors to consider when you're selecting the device: cost, insurance are paramount. We can't do much about it, but they do have programs to help if the patient can't afford it. There are physical and cognitive issues. Nursing home patients often will, after a hospitalization, may have cognitive issues. A bunch of scales can be used to help us. Arthritis – people with bad hands can't squeeze off the MDI. Similarly, poor strength and dexterity, you need about 7 pounds of pressure to activate an MDI. People with Parkinsonian tremors can't do it. And then there's patient preferences. Some people hate DPIs because they don't like the taste of the powder in their mouth. Others don't like MDIs, they have trouble with it. Some prefer a nebulizer. So age is important. And of course we'll talk a little bit here now about this peak inspiratory flow rate, or PIFR, particularly in so far as using dry powder devices. So a low peak inspiratory flow may lead to reduction in the medication actually reaching the lung and lung deposition. So a low peak inspiratory flow rate about 30 liters, and that can end up in the mouth. As high as 60 effectively will reach your lungs. Most DPI devices require at least 30, and 60 would be best. Now, we've been testing this, and particularly in frail patients and a lot of women of short stature with low lung function can be at risk. Primarily though it's people who are frail, so just be aware of that. So now I'd like to turn it over to my colleague, Nic Hanania, who is an associate professor of pulmonary and critical care medicine and director of the Airways Clinic Research Center at Baylor Medical College. Nic, welcome.

Dr. Hanania:

Thank you very much, Jim. And it's a pleasure to be here and to discuss pharmacotherapy of COPD and where are we with bronchodilation and now we have triple therapy. And Jim did an elegant introduction of why we need more therapy for this significant disease in the year 2019. Let's first revisit the goals of management of COPD. And certainly as clinicians, we always strive to do better, and we want to get our patient better. Certainly we look at lung function. Improvement in lung function is very important, but also reducing symptom burden is important, as well. Reduction of exacerbation and also reduction of functional limitation, improving health quality, as well as exercise tolerance, and ultimately we want to reduce admission to hospital and mortality, a major outcome that has been actually haunting us and our patients. COPD now is the fourth largest – fourth common cause of death in the United States. But let's remember, just like Dr. Donohue mentioned with inhaler devices, it is also important when you reassess therapy, that it's not enough that you do it one time. There is a continuous need for reassessment of therapy and adjusting therapy, so this is not a one-time deal. And this is important for the patient to understand, but for us as clinicians to understand when we meet with COPD patients, particularly those with moderate to severe disease. So what do we have? Pharmacologically, we have several drugs now on board, and many of these drugs have been shown to actually fulfill some of the goals that I just mentioned; improving lung function, minimizing symptoms, improving quality of life, and preventing exacerbation. But more now in 2019, we believe that it's not a one-size-fits-all. So some patients may improve with some drugs, others may improve with others. So it's important before stepping up or modifying

treatment to re-evaluate the treatment goals, looking at what the patient is expecting from us, the clinical phenotype of patient, also the presence of absence of comorbidities may influence which choice of medication you make, but of course adherence. It's certainly important to involve the patient in shared decision-making when it comes to prescribing therapies that we are going to talk about. Of course this is a busy slide, but you can see that we have a huge armamentarium and more to come of medicines for COPD. Of course we don't throw all these medicines to the patient, but it is based on the severity. Bronchodilators constitute the majority of patients – of drugs that we use for treatment of symptomatic COPD, but we also, as well, entertain using inhaled corticosteroid, but also other medications for the more severe patients. So, where do bronchodilators play a role in COPD? Well, you know, the two most common types of bronchodilators we have pharmacologically are the beta-2 agonists and the anti-cholinergic. And as you see on this slide, these drugs do not work on the same pathway; thus, there is no reason to believe that one is exclusive of the other. In fact, there is quite a bit of interaction between beta-2 agonists and the long-acting muscarinic in clinical trials, and even now in animal models to believe that there may be even a synergistic effect. Beta-2 agonists, just to remind you, work on activating the beta-2 receptor of smooth muscles, causing relaxation of the smooth muscle cell of the airway. Anti-cholinergics block the M3 receptors. These are muscarinic receptors on the smooth muscle, and cause relaxation through that pathway. So different pathways; and therefore it is not unheard of to see that combination of anti-cholinergics and beta agonists have actually been gaining more popularity in the treatment of COPD. Indeed, there are data; this is a current opinion paper showing the fact that in the non-treatment patients, which is shown on the left of the slide, patient's beta-2 receptor or sympathomimetic activity and cholinergic activity are very active. So blocking the cholinergic activity or activating the beta-2 receptor can actually have smooth muscle relaxation, and there maybe some synergistic effect, as well. So let me review the evidence that we have on the use of LABA/LAMA. LAMA being the anti-cholinergic long-acting agents, LABA is the long-acting beta agonist. And now we have actually five approved LABA/LAMAs in the United States, either given once a day as you see on this slide, or twice a day through different devices, delivery system by powder inhaler or metered dose inhaler. Now, there are several papers, and thus we have now meta-analysis showing consistently that two drugs working through different mechanisms are usually superior to one drug working through one mechanism like LAMAs versus LAMAs in this case, on lung function. Of course, lung function is important and there is quite a bit of evidence that bronchodilation-wise, when you have two together, they're better than one. But we also know that bronchodilation may also influence other outcomes, including exacerbation, but also patient-reported outcomes. And in this slide, if you look in the graph in the middle, you can see that LABA/LAMA therapy actually may have superiority to monotherapy on different outcomes, including exacerbation, but also symptoms of the patient. And looking at symptoms, there are different studies with different ages that we have now. The one on the left you look at tiotropium/olodaterol versus tiotropium alone. And looking at the CAT score, which is a scoring system we use for assessment of symptoms, on the right of the slide you see that another combination therapy here, umeclidinium/vilanterol, another LABA/LAMA. Looking at a different PRO here, looking at the Transition Dyspnea Index, which is a measure of dyspnea, both show consistently that a LABA/LAMA here improved symptoms and decreased dyspnea. And it's interesting in some of these studies show that the higher the baseline dyspnea, the higher the symptoms that a patient has, the better effect in reducing these symptoms with a LABA/LAMA combination. More interestingly now, we believe the lungs and the heart are very well interacting, and in patients with COPD, they often have cardiovascular morbidities. And it has been shown now that LABA/LAMA interact very well in improving or decreasing hyperinflation in the lung, and may indeed improve cardiac function; left ventricular volume can be decreased, and cardiac output may be improved. And while these studies are only small, they actually may put a very important emphasis on this type of treatment in patients, particularly those with underlying cardiovascular disease. Of course, safety of these drugs has also been well documented in at clinical trials. What about LABA/ICS? And we know that combination therapy is now very popular in both asthma and COPD. We talked about one of them, which is the LABA/LAMA combination. What about the LABA/ICS? Or inhaled steroid long-acting beta agonist that's another option for some of these patients. And we indeed have these three approved LABA/ICS combination therapies in the U.S., and we often use them in patients with high risk of exacerbation. While there's some marking evidence showing that LABA/LAMA may actually reduce exacerbation in this large study called the FLAME study, which was a one-year-long study, where they showed that even in moderate patients – moderate to severe patients with COPD who have high risk of exacerbation, adding a LABA/LAMA may actually be superior in reducing exacerbation compared to LABA/ICS therapy. In fact, it was in this study they looked at other outcomes, and in every other outcome, PROs, or patient-related outcomes, the LABA/LAMA combination was superior to the LABA/ICS, and obviously that's important to know because the presence of ICS in the regimen may indeed increase risk of potential side effects long term, although there is an important role for ICS in the more severe patients with high risk of exacerbation, possibly high eosinophil count at baseline. And there is actually a meta-analysis now comparing a LABA/LAMA versus LABA/ICS on exacerbation, and you can see that there is a trend favoring a LABA/LAMA in general over LABA/ICS on exacerbation and reduction. Finally, what about LABA/LAMA versus LABA/ICS on lung function improvement? In this meta-analysis, it looked at lung function improvement at 12 weeks, but also at six months and, in both occasions, LABA/LAMA tends to have superiority over lung function improvement. Not surprising because you're using double bronchodilation here versus one bronchodilator and an anti-inflammatory. So, in summary, what we know about LABA/LAMA now is the combination of two bronchodilators with two mechanisms of action can indeed help maximize bronchodilation, but also improve symptoms and reduce

exacerbation compared to monotherapy, and potentially, in some cases, it is more superior than LABA/ICS. What about a triple therapy? Just briefly, we have now one approved triple therapy in the United States and one in Europe; a different one, as you see here, and a third one being studied in Phase 3 trials containing different varieties of ICS, LABA, and LAMA. Where is the position of triple therapy? We often see these patients who have severe disease so the LABA/LAMA may not be enough where you have to add an inhaled corticosteroid. I think one of the major studies that has been published in the last couple of years is the IMPACT trial, which was a study looking at triple therapy in one device given once a day, compared to LABA/ICS versus LABA/LAMA over one year in high-risk exacerbated patients who are symptomatic. The study is well published, multiple sub-analyses have been published, but the bottom line, the main outcome of this study was exacerbation – moderate to severe exacerbation over one year. And as you see on the left side of this slide, the study met its primary endpoint in a way that triple therapy reduced exacerbation more significantly than LABA/LAMA or LABA/ICS. So in this high-risk population, a triple therapy may actually have an advantage in reducing exacerbation, but also prolonging the time to first exacerbation. Similarly, when you look in the same study on the quality of life measured by St. George's Respiratory Questionnaire, the odds ratio of being a responder as you see on the slide on the right side of the slide on the bar graph, the ratio of improving quality of life was better with the triple therapy versus dual therapy of LABA/LAMA or LABA/ICS. What about safety? I talked about inhaled corticosteroids. In this study, they did find a high risk of event of pneumonia with triple therapy, naturally expected with an ICS-containing agent compared to a LABA/LAMA alone. The LABA/ICS compound also was associated with increased risk of pneumonia. Although these pneumonia episodes were not significant enough to cause hospital admission, but they're something that one has to keep in mind. There were no other adverse events like regarding cardiovascular effects or other significant adverse events reported. Well, the same thing has been done with other triple therapies, but just for the sake of time, just to show you that there have been several large trials published now where the triple therapy that is approved in Europe and not in the United States, showing an advantage in reducing exacerbation and improving patient-reported outcomes in patients who are severe enough that need triple therapy. And then finally, more recently, the triple therapy that is now in Phase 3 trial has been tested in this large trial. Although it was a short-term trial, there was improvement in lung function and additive improvement compared to dual therapy with a triple therapy given twice a day. But also surprisingly, even though this was a very short study, there was a reduction in exacerbation in that small short study, even though that was not the primary endpoint. So we are awaiting the Phase 3 trial that is now being done and completed. So in summary, where we are with triple therapies in COPD is that we have an advantage over dual therapy in selective patients. And I know Dr. Han is going to discuss some of these criteria where triple therapy may fit nicely. It may not be an option in all patients, specifically not in the mild/moderate disease patients. One has to be cognitive of the inhaled corticosteroid effects, but also potential adverse effect in selective population, increasing risk of pneumonia, long-term effect on bone density, and increased risk of other side effects like cataracts. With that, Jim, I'd like to turn it back to you.

Dr. Donohue:

Dr. Hanania, thank you for sharing those insights with our audience. A brief reminder for our audience, we encourage you to participate by submitting questions for our panel using either the Q&A box, as seen on your screen, or through Facebook or Twitter by using #COPDbroadcast. Last on the panel, but certainly not least, we're going to hear from Dr. MeiLan Han, who is a Professor of Internal Medicine at the Division of Pulmonary and Critical Care at the University of Michigan in Ann Arbor. And MeiLan, the floor is yours. I'd like to also say MeiLan was on the committee that makes the GOLD recommendations, so thank you for that.

Dr. Han:

Thank you so much. So, right now what I'd like to do is combine everything that Dr. Donohue and Dr. Hanania so nicely put together for us, and figure out how does that apply to individual patients. How do we create treatment strategies on an individual basis? So if we go way back, and I mean way back to 2001 actually, GOLD really was just completely driven by spirometry. In 2011, we saw one of the biggest update that we've seen in awhile, and this is to create the ABCD categorization system. And the attempt here was to combine both spirometry symptoms and exacerbation risk to put every patient into a box, A, B, C, or D, and then development treatment strategies from there. And I think there's a lot of really good things about this, but in 2019, well actually 2017 and then 2019, we saw even further revisions to this. And this is really all about the data that is coming in that allows us to personalize treatment strategies for patients with COPD and focus really either on symptoms or on exacerbation history. Now that's not to say that spirometry isn't important; spirometry is clearly still important. We need it for diagnosis, we need to have the presence of airflow obstruction, and it does help us to grade severity of patients, which is really important for figuring out, for instance, which patients should be considered for advanced therapies. Well, when it comes to things like how do we alter pharmacological management is really important at this point than to think about symptoms; shortness of breath, quality of life, and then also exacerbation separately. And the new goal and strategy really encourages us to think about both of these kind of axes, if you will, for individual patients. So we have the – in 2017, we had this split of spirometry from the symptom and risk assessment. That doesn't mean, again, that spirometry is not important, but it's been split out. So we still have the GOLD 1234 that everyone is really familiar with. The ABCD has been tweaked in that spirometry is no longer part of it. So we've got low symptoms, the A/C group, high symptoms, the B/D group, and that's based either on MMRC or CAT. And

then low risk and high risk for exacerbations, and that's based on prior history. Either 0-1 moderate exacerbation in the prior year, or 2 or more moderate, or 1 or more severe, pushing you up in this C and D category. Now one of the things I think a lot of people do not realize is that the ABCD categorization is really only intended for first assessment. This is to help you understand and make a decision about what the initial pharmacologic therapy for patients is. Now it was not our intent to change this from the 2017 version, but we do add some clarifications here on where we think patients are most likely to benefit from one strategy versus another. So a bronchodilator is still a great treatment option, short-acting or long-acting, for Group A. But for Group B, where they're really having persistent symptoms, this is where you need to think strongly about a long-acting bronchodilator like beta agonist or muscarinic antagonist. Now, while it's not there on the graph you're looking at, if you look down in the text, the text does say for patients that are having really high symptoms, like let's say CAT greater than 20, LABA/LAMA combination therapy actually can be considered for first-line therapy for Group B. For Group C, LAMA therapy is recommended as initial treatment. But this in Group D is where we really start to personalize our management strategy for patients. LAMA is still a great option, particularly if this is initial management. But if you have a patient with really high symptoms, LAMA/LABA therapy may make sense. Or if you have patients with high eosinophils, and that's defined as 300 or more, you may want to think about ICS/LABA as initial therapy for your Group D patients. So, how does this actually fit into perhaps a real patient? So, I would like to walk you through a couple of cases now. The first is Mr. F. It is a 58-year-old gentleman who presents with increased dyspnea on exertion, and he was diagnosed with COPD about five years ago. At that time, he was felt to be Group B, started on LAMA therapy. His FEV1 at that time was 65% predicted, but his CAT is still 15 despite therapy. So, this patient is really struggling with dyspnea. Can we do better than LAMA alone? One of the updates for the 2019 GOLD document is the concept of the management review cycle. Now this is actually something that was inherent to the GINA document for asthma for a long time, so it's something we sort of stole. But I think it's a great idea, and something that I think we as clinicians naturally do, but it's important to kind of remember, and it's nice to have this little trigger here for us. So the first thing to do is I always talk to my patients about their symptoms and their exacerbation. If you're like me, your patients may be seen elsewhere, which means all of those exacerbations may not always get documented in my electronic medical record, so it's always important to go to the source, talk to the patient, find out if they've had any episodes requiring – breathing episodes requiring treatment with antibiotics, steroids, or both, or have landed them in the ER or hospital. The next thing is to assess. We don't want to totally throw away or disregard current therapy if it's not being applied appropriately. So that's where we want to take this opportunity to reassess inhaler technique and to talk about nonpharmacological approaches like pulmonary rehabilitation. But if that's all been applied, the patient is adherent, they're using the inhaler right, then it may be time to adjust. And here, we need to think about symptoms, exacerbations, and potentially also which inhaler device would best suit the needs for the individual patient. As Jim had alluded to, unfortunately adherence to COPD medications can be poor. Believe it or not, if you look at all of the chronic diseases that we care for, diabetes, etc., adherence to respiratory medications is one of the absolute worst. And I have to admit, I don't fully understand why that is. I suspect it may have something to do with co-pays, it has to do with things like patient thinking they can stretch their medications out, that they only need to take them to relieve symptoms, and don't fully understand that the regimens we have them on are actually meant to be preventative, as well. And unfortunately, the consequences of poor adherence can be quite significant. So beyond symptom control and worsened quality of life, they may have more frequent exacerbations, more frequent hospitalizations and, as the data shows here, may actually have higher mortality. So it's really important. And I think the onus is on us to a certain extent to really educate our patients that it's important to take their medications as prescribed. So if it's twice a day, that means they take it twice a day and that they don't skip days. And there's actually several recent studies that support a couple of different strategies. So first, we talk to the patient and explain to them why it's important, and then we look at the regimen; is there something about that regimen that's making it hard for the patient. Would it be better to do once a day versus twice a day? Is there an issue with the delivery device? Would it be better to combine medication into one? And there's actually now a variety of monitoring devices that can be placed on inhalers, as well, if this is something that you and the patient decide would be helpful. So, again, it's important to monitor and to follow up at each visit to run through that list again to make sure you understand what the patient's been on. I don't know about your practice, but all too often in mine, the patient has been switched due to a change in formulary; it happens all the time. So this is a great opportunity to bring the patients in, find out what are they actually taking, and then this is your opportunity to retrain the patient on that device. And then once you're confident that they can use the device, etc., then you can talk to the patient about whether a different medication or set of medications might be helpful for them. So in this case, our case that we've been talking about, this patient is really struggling with dyspnea. And they're on a LAMA alone. So what are our options? Well, if we look at the GOLD 2019 update, they actually have very specific recommendations and a little bit of a flow chart to follow if the issue is dyspnea versus exacerbation. So, as you can see on the flow chart here, the next step up would be LABA/LAMA dual therapy. This has been available as a single inhaler in the U.S. market for the last several years. If, despite LABA/LAMA therapy, the patient is still having symptoms, this is again where you want to go back in, you want to assess so they're on the right device; maybe they need to be switched over to a nebulizer, etc. And interestingly, this is I think the first time we've really seen this in the GOLD document, they also introduce the concept of step-down therapy. So if a patient, for instance, was on LAMA/LABA/ICS or LABA/ICS and it really wasn't helping, this is the opportunity to actually maybe even completely switch over to a LABA/LAMA

therapy. So Dr. Hanania has already very elegantly walked you through a lot of the data on why dual bronchodilator therapy can be so incredibly effective, but this is just again to show you that dual therapy results in greater improvements in symptoms here on the left panel with respect to COPD assessment test for the CAT, and the right panel with respect specifically to the BDI/TDI, which is a dyspnea index. This is a meta-analysis that shows the dual bronchodilation actually improved exercise capacity over the monocomponent. And ultimately, this is the kind of thing our patients really care about, right? They want to be able to, you know, go to the playground with their kid, they want to be able to get to the mailbox in some instances, or just go out to dinner comfortably. So it's really a combination of improving shortness of breath and exercise capacity that we're really looking at when we maximize dual bronchodilation. Now what about our frequent exacerbators. So that's our Group D. I want to introduce you to Mrs. T. She's a 70-year-old woman with an FEV1 of 35% predicted. She presents to clinic following a hospitalized exacerbation. Now previously, she had been on LABA/LAMA therapy. Despite that, her CAT is 19. She does have an eosinophil count of 300. And additionally, she had one additional moderate exacerbation in the past year. So what do we do with Mrs. T? So again we go back and now we see there's a whole separate – on the right-hand panel, a whole separate flow diagram for what to do with exacerbations. Now, believe it or not, the arrows actually looked worse at one point. We did our best to clean it up. I realize it looks painful, so I want you to kind of forget about that for a second and just walk it through together from kind of a common sense standpoint. So patients on a single bronchodilator, or potentially dual bronchodilator in this case, so where do we go? Well, the evidence suggests that there is a role in these patients potentially for triple therapy. Dr. Hanania already walked you through a couple of those slides. This slide is just meant to tell you that there are actually three separate development programs going on across the world with three separate kind of triple combination in a single inhaler therapy. The only one that is currently approved in the U.S. is the one in the middle. This is the IMPACT Development Program that Dr. Hanania already spoke to you about, but I did want you to be aware of some of the data that is actually very parallel to the IMPACT data. So what you can see here is IMPACT on the left, TRIBUTE again not approved for use in the U.S. currently, but it shows a similar pattern of maximal exacerbation reduction when patients are on triple combination therapy, as compared to either of the dual combinations. Now, what's really interesting is that we're really seeing a consistent pattern coming across several of these studies for a linear relationship with respect to exacerbation reduction and inhaled corticosteroids. So, on the left you see data from IMPACT, and here you have the three arms, and the two lower; the blue and the orange bars relate to the two steroid-containing arms. And you can see here that once right around maybe 100, the signal starts to split and you may develop increased risk of exacerbation in the green arm, which is the LAMA/LABA arm, as eosinophils get higher. But that risk remains lower in the inhaled corticosteroid arm. So this is why GOLD has come out and said, "Well, we think above 300, probably those patients really benefit. Below 100, probably those patients are less likely to have benefit. And 100-300 is kind of a gray zone." But I think it's really important to see the data for yourself and realize these are not exact, you know, written in stone tablet thresholds. These are us kind of interpreting the data that we're seeing. Now on the right-hand panel, you see on the top lung function improvement, and on the bottom exacerbation. This is from the KRONOS and ETHOS development programs. And the data here is a little bit more jaggedy, right? And they actually used a different model. But it's the same concept that the exacerbations risk is mitigated with the inhaled corticosteroid, particularly as exacerbations go up. But again, it – there's that relationship, but it is hard to say absolutely one specific number the risk suddenly flips on a dime. It doesn't. So again, this is where the art of medicine comes in again. And this is why, if you look on the exacerbation panel for GOLD now, you'll see these tiny little asterisks. And what those tiny little asterisks are telling you are that ICS, you may want to consider that more particularly for the patients with the higher eosinophil counts, but at the same time, we also want to think about risk mitigation. And so for patients on inhaled steroids, some of the patients are going to be at increased risk for pneumonia. This is data from a meta-analysis looking at the triple therapy programs and pneumonia. And you can see pretty much across the board, there is a slight but real increase in pneumonia rates as compared to the non-steroid-containing arms. From prior work, we know that the higher the dose and the longer patients are on inhaled corticosteroids, the risks go up. So if you have a patient that is having problems with frequent pneumonia, and you've got them on an inhaled steroid, and particularly if their eosinophil count is low, you may want to think about getting that patient off. For the first time in the last few years, we actually have developed some evidence to guide inhaled corticosteroids withdrawal. There are two trials; these include SUNSET and WISDOM. And in both of these studies, patients were on triple therapy and then the inhaled steroid was withdrawn. And what we can see is that, overall there was actually not a big difference in exacerbation frequency in entire patient population once steroids were withdrawn. But if you cut the patient populations by eosinophil count, and SUNSET is on the left and they use 300, WISDOM actually shows you a variety of cut-points on the right. But once you get around that 300 or 400 range, this is really where the risk for increased exacerbations comes in with the withdrawal steroids. It's consistent with the data that I showed you, but I think it really does help to provide an evidence basis for clinicians to help decide what to do for an individual patient. So as you can see, it's really all interconnected, right? Our patients lung function directly relates to dyspnea, relates to cardiac function, like Dr. Hanania pointed out, and then we've also kind of on the right side – we've also got to be thinking about balancing infection versus exacerbations and the type of inflammation in an individual patient. But I have to say overall I'm quite excited about the new data that we have, and I think it really does help to guide us in choosing the right therapies for the right patients. At this point, I'm going to turn it back to Dr. Donohue.

Dr. Donohue:

Thank you, MeiLan, for a really terrific presentation. So we'll be now getting back to you all with questions. So I really want to thank both of you, Nic and MeiLan, for your thoughtful presentations that painted a really very clear picture tonight about COPD. And now I'd like to bring the audience into our discussion since they've been sending in some really great questions based on the information that has been presented here tonight. So, we'll be asking each of you to comment on the various questions that come up. So, we're going to start with a question: What impact, if any, do comorbidities have on treatment selection? For example, I'll start with you, MeiLan. If my patient had comorbid primary pulmonary hypertension, a terrible problem, how would I approach designing their treatment plan?

Dr. Han:

Yeah, that's a great question. Unfortunately, as you know, these patients tend to have a very poor prognosis. At least at my institution, I always co-manage them with cardiology. The first thing though is to think about it, right? We're getting a lot more CT scans, you can see those dilated pulmonary arteries, or if I have patients that have dyspnea out of proportion to what I would have expected based on their lung function test, I think about getting that echo. I think that's the first step. Nic very nicely demonstrated some of the data that suggests that maximizing bronchodilation can actually improve cardiac function. So for me, that's probably my next step, and then to work with cardiology on whether other PH-specific therapies might be appropriate.

Dr. Donohue:

Alright, thank you very much. And Nic, do you have anything to add to this?

Dr. Hanania:

Well not essentially on pulmonary hypertension patients, but comorbidities in general are very common, yet underdiagnosed and undertreated. And I think I want to take that opportunity to emphasize that, yes, we as pulmonologists focus on the lung, but all these other systems are important. For example, anxiety and depression, osteoporosis, cardiovascular comorbidities are very important. And yes, they may affect the course of the disease and they may actually influence our selection of therapy; for example, somebody with underlying arrhythmia, one has to be cautious with these anti-cholinergic and beta agonists. Somebody that has increased risk of pneumonia, one has to be cautious with the selection. Somebody with cognitive dysfunction, I will have to be very – like you mentioned, very careful in selecting the appropriate delivery system. So I think it's important for us to do the holistic approach of this disease.

Dr. Donohue:

Remember, many patients have concomitant sleep apnea, for example, as a problem with pulmonary hypertension really isn't too much related to COPD, or they have pulmonary embolus and things like that. So, as both of you were saying, a comprehensive kind of evaluation is essential. Now the next question, and we'll start with you Nic, do you have any specific counseling points for individuals with COPD who have not been able to quit smoking? That's my entire practice.

Dr. Hanania:

I don't have a million dollar answer for this, but it is a very important step. I mean, that's actually the most important thing you can do is to get them to stop. And it's not a one-time deal. And one has to try and try and try. Of course, we don't want to offend, as some patients get offended, so you have to do it in a politically correct manner. But, you know, the 5 A's that are recommended by the smoking cessation practice guidelines are important, but some patients are not interested. Maybe there are some ways of discussing what are the barriers about getting them off. Offering a pharmacological therapy to help them come off cigarettes. It's very hard to come off cold turkey. There are nicotine replacement or other agents are important. Discussing the economic impact and the health impact of smoking is very important. So there are a few things that we've done. Obviously, I can't say we were 100%, you know, successful, but it's a matter of checking it more than once. And, by far, more than any of these medications we talked about, smoking cessation has been shown to reduce reduction in lung function decline, as well as mortality in these patients, as you all know.

Dr. Donohue:

I'm very pleased to hear you – I know you're both very fine, sympathetic patients, but your patients do not discharge the patient, or "You're still smoking, get out of here." You're saying you go over and over, and that's what I do, say, "Regardless of what you do, I'm still your friend. I'm still going to try to help you." MeiLan, do you have any – how do you handle these all-too-common individuals?

Dr. Han:

Yeah, it's just that we all shared, and it's interesting actually earlier today I had the opportunity to chat with some actual COPD patients, and we were talking about things they wished that had potentially been done differently. And unfortunately I think that some of them didn't quite fully understand the continued lung function loss that can occur with continued smoking, so at least getting that education piece out there. I think there is actually some data suggesting the number of times that we actually bring this up with the patient, and the number of times that they try to quit overall increases the likelihood of success. So, I – you know, it's just sort of my approach, but I try to be a cheerleader as opposed to – that's sort of my general approach. So, as Nic mentioned, I think for many patients, really it's sort

of a root cause analysis of what is actually driving them to smoke and unfortunately for many of my patients it's stress. So trying to figure out who I can work with in the mental health group to, you know, additional medications or counseling, etc., to get the stress managed, I think for many patients it's a key element to helping them manage this second, then manage the smoking.

Dr. Hanania:

And one of the most important things that can help alleviate stress and anxiety in these patients is exercise.

Dr. Han:

Yeah.

Dr. Hanania:

Getting them involved in – may not even, if we can afford sending them for rehab, even walking is very important.

Dr. Han:

Yep.

Dr. Donohue:

Okay, well MeiLan, we'll stay with you. The next question: What are the most common side effects you see in patients utilizing triple therapy? Now, we've had about a year's experience with the United States product, so what are you seeing? I'll ask you, Nic, also on that.

Dr. Han:

Well, I think we already had a lot of data on bronchodilators. So we know those can cause some dry mouth and things like that. But there's actually not tons of safety concerns, at least in my mind, with respect. So it's really – it's the inhaled steroids that we're talking about. And the data that's coming out, and the biggest thing we worry about, which I mentioned, is pneumonia. It's really very similar to the triple therapy versus the duals – I showed that meta-analysis. The risk is there; it's not huge, but it's there. So that's where I think it's important to really personalize. We know things that increase risk; older age, prior history of pneumonia, lower lung function, etc. So, honestly, I think that's the thing I worry about most. Now, there are data on a few other things. We've all seen patients with thrush and, you know, hoarse voice like I have today, although that's not related to inhaled steroids. That can be bothersome for some patients, and sometimes just changing the molecule or device may be helpful. The other things that we actually have some accumulating data on are other things like bone density over long-term, cataracts, and I actually think there was a recent article on microbacterial infections, as well. So these are lower risk. Some of these things really accumulate the longer patients are on inhaled steroids. But I think they're all important to keep in the back of your mind. And I always have discussions with patients before I start an ICS. These are all the things I'm hoping to get out of this, but just so you know, these are all the things that we need to be alerted for.

Dr. Donohue:

Nic. Thank you very much.

Dr. Hanania:

My experience is the same. I would like to emphasize the topic of side effects because those can be neglected and we have to advise the patient to rinse their mouth and spit out, you know, with inhaled corticosteroids. I haven't seen many urologic problems, but it's been reported with anti-cholinergic that urinary outflow obstruction can happen. You know, again, clinical trial data which we shared are based on clinical trials, and the longer we use these drugs in real life, the more potential safety either hazards or reassurance that we get. But in general, in my practice, it has not been an issue. We always have to weigh risks and benefits and decide to go for the drugs or not.

Dr. Donohue:

Okay, so sticking with you, Nic, the next question: What specific differences do you see in disease presentation and disease course among the different underlying causes of COPD? So we have – it's a tough question.

Dr. Hanania:

Well, if I understand it right – but I mean, I think I'm going to take the opportunity to maybe talk about disease phenotypes.

Dr. Donohue:

That's alright. That's what we want.

Dr. Hanania:

Okay good.

Dr. Donohue:

So, tell me about the different presentation –

Dr. Hanania:

So, for many years, we thought COPD was a one-phase disease, and actually no, not really; they told us it is a blue bloaters – so two-phase diseases. We also thought about it as a disease of the old and the disease of men. Well, we know now that none of these are true. That how long ago did you see a pink puffer or a blue. We do see them, the pure emphysema and pure chronic bronchitis, but actually they are more than that. So phenotypes there are can be clinically defined. One that is easily defined is the frequent exacerbated phenotype. I think that is very important. The chronic bronchitic phenotype. So those are identified by taking a good history. And it has been shown that chronic bronchitics, those with cough experienced them to have high risk of exacerbation, and there are certain drugs that may help these patients compared to those who are just breathless, those dyspneic patients who don't have cough and sputum every day. The frequent exacerbators, that's the type of patient we want to target with LABA/LAMAs, LABA/ICS, or even triple depending on the different biomarkers and characteristics. Even now, really interesting, you know, radiologic biomarkers that can actually help us subdivide these patients even further. So I think we're getting there. We're not there yet. We're getting to a bit more personalized approach to this disease by identifying these phenotypes.

Dr. Donohue:

MeiLan, since you're a writer of GOLD, I'm going to add you. One of the things I've learned from you was not just in the earlier levels of GOLD, but as you get into more advanced, previous cigarette smokers would make you think about a specific type of fifth or sixth drug, ex-smoker, mucus hypersecretion, chronic bronchitis, so tell us a little bit about that. Because that's in GOLD, and it's really good stuff.

Dr. Han:

Yeah. Yeah, and we didn't have time to get into it in the earlier presentation, but if you've got patients that are failing their regimens, we do have a couple of options; PDE4 inhibitors are an option, but they really only help patients with frequent exacerbations and chronic bronchitis like Nic was saying. And also there is azithromycin, which my group helped to demonstrate its effectiveness as part of an NIH-sponsored study. The thing I always think about are taking to my – counseling my patients about long-term risks and making sure they don't have underlying MAI, checking EKGs, and hearing. But all of that aside, it does seem to benefit patients with respect to exacerbation reduction, but interestingly, and I think you were alluding to this, the data suggests that it doesn't help current smokers, or at least that's what we saw with the NIH-sponsored study.

Dr. Hanania:

If I may add, another group like emphysema patients, they –

Dr. Donohue:

Next question: Are there any clinical situations that you see really as exceptions to the GOLD guidelines?

Dr. Hanania:

Well, we have not talked about the non-pharmacological approaches. And in some selective patients with emphysema, surgical therapy may be important –

Dr. Donohue:

That's what you're saying about –

Dr. Hanania:

Bronchoscopic interventions are important. And I think those have to have a very important role in that specific patient population. That's where CT scans and measuring lung volumes may play a role in identifying that subgroup of patients.

Dr. Han:

We actually don't like to refer to ourselves as the GOLD guidelines; we're like the GOLD management strategy, the recommendations. We fully recognize that not all patients are going to actually fit the nice boxes, right? And try to really give people a lot of leeway, help them understand what the thinking was, but then, you know sometimes the patients don't always fit the boxes.

Dr. Donohue:

Great. Thank you both very much. Now, based on the questions received, I'd like to ask both of you to just reflect on what is your final take-home message to our Reach MD audience? So, we'll start with you, MeiLan. There's a lot we have to digest, and you guys have covered so much.

Dr. Han:

Yeah. Well, I think my one take-home message would be, despite the fact that I think there are incredible benefits with triple combination therapy, we really should not be considered as initial therapy; they are not first-line therapy for most patients, and are not

really right for all patients. I think we're getting a lot more information on which patients are and are not benefitted from inhaled corticosteroids. And I really encourage physicians to really try to personalize management. We really want to maximize the benefit and risk in individual patients.

Dr. Donohue:

Thank you very much, MeiLan. Nic, what would be your take-home message?

Dr. Hanania:

Well, I want to take the opportunity to reach out to my colleagues through this nice technology to keep COPD on your radar. It's something that we didn't talk about, and it's underdiagnosed; we don't think about it, especially in our primary care settings, as patients have other medical problems. Think about it in patients who are above 40 who smoke, and have symptoms. It's not a disease of the old, and it is not a disease of men, and it's not a blue bloater or pink puffer. It may not look blue or pink. And I think spirometry, I want to take opportunity to preach – spirometry is very important to make the diagnosis early and assess how severe is the disease and start with some nonpharmacologic approaches and then go with some of the pharmacologic approaches, depending on how severe is the disease. The good news is we have hope for these patients. We can't cure the disease yet. And we have to change our disinhalistic for many years about this disease.

Dr. Donohue:

Thank you, Nic. And the last thing I'd like to say would be just we now see we're closing in on the year of personalized medicine in COPD and, based on the really tremendous information both of you have been generating, which you shared with us tonight. Well, with those closing thoughts, I'd like to thank our panel for presenting alongside me today and discussing this important topic. Dr. Han and Dr. Hanania, it's great sharing the floor with both of you. And thank you very much. Also, I'd like to thank our audience for their participation in this program. I'm Dr. James Donohue for Reach MD, encouraging you to be part of the knowledge. Thank you for joining us.

Announcer:

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