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

Addressing the Unmet Needs of Refractory Chronic Cough

Announcer:
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Dr. Eggert:
Welcome everybody to this ATS activity, “Addressing the Unmet Needs of Refractory Chronic Cough.” Our faculty today for this activity include myself, Lauren Eggert. I’m an Associate Professor of Clinical Medicine in the Division of Pulmonary Critical Care, Allergy, and Sleep Medicine at the University of California, San Francisco, in San Francisco, California. And now I’d like to introduce my co-faculty to have them introduce themselves.

Dr. Dicpinigaitis:
Thanks, Lauren. I’m Peter Dicpinigaitis. I’m a Professor of Medicine at the Albert Einstein College of Medicine in New York. I’m also the Director of the Montefiore Cough Center at Montefiore Medical Center in New York.

Dr. Eggert:
So I just want to start with a disclaimer. This activity is intended for healthcare professionals for educational purposes only. This content reflects the information available at the time of development and may not represent the most current evidence, regulatory status, or prescribing information. Always consult current prescribing information, clinical guidelines, and institutional policies before making any clinical decisions. And we’d like to generously thank GlaxoSmithKline for an independent medical educational grant provided to support this informational activity.

Our learning objectives today are threefold. First, is to summarize the best practices for the diagnosis of RCC, or refractory chronic cough, in conjunction with current evidence-based guidelines. We’re then going to describe the underlying pathophysiology of RCC in accordance with the current understanding of the mechanisms involved in cough hypersensitivity. And we’ll finish up with assessing the ongoing developments in clinical research for emerging therapies to examine their potential impact on improving patient outcomes in RCC.

So during our time together, first we’ll start with an introduction and some preliminary data gathering. We’ll talk about improving RCC diagnosis in accordance with evidence-based guidelines. We’ll then talk about the underlying pathophysiology of RCC, and finish up with emerging approaches for addressing the RCC disease burden and improving patient outcomes.

Alright, moving on. Improving RCC diagnosis in accordance with evidence-based guidelines. To talk more about diagnosing refractory chronic cough, we first have to understand what refractory chronic cough is. So, chronic cough is any cough lasting longer than 8 weeks. It can be classified by its clinical characteristics, such as a dry cough, a wet cough, the amount of sputum production, the duration of cough, severity—mild, moderate to severe and interrupting activities of daily living, and also the etiology.

Refractory chronic cough, though, is a cough that persists despite proper evaluation and treatment of the underlying etiologies. And

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chronic cough is really only one type of cough. We categorize cough by duration into three categories. There's acute cough when you're acutely ill, usually with an acute viral upper respiratory infection, usually with an acute viral upper respiratory tract infection, and this lasts less than 3 weeks. Then, in between acute and chronic, there's a subacute cough. This is a cough that usually lasts 3 to 6 weeks, sometimes up to 8 weeks. The most common cause for a subacute cough is a post-viral cough. After you've had an upper viral respiratory infection and you just have persistent cough. Other etiologies of cough in the subacute category include pertussis, and it can be even that pre-chronic phase. But once you get into longer than 8 weeks, it's categorized as a chronic cough. And the most common etiologies of chronic cough are postnasal drip or upper airway cough syndrome, asthma, nonasthmatic eosinophilic bronchitis, and gastroesophageal reflux disease.

Now let's talk about the epidemiology of chronic cough. Chronic cough is extremely common. It impacts, depending on the study, probably somewhere between 10 to 12% of the general population. Females are more likely to seek medical attention over males in about a 2:1 ratio, and it most commonly presents in adults in their 50s or 60s, but can appear at any time. And so, chronic cough, that cough lasting greater than 8 weeks, about 10 to 12% of the population, at least 5% in the U.S., although it varies by country and area of the world, as you can see in this graphic. And then the majority of chronic cough, probably 90% of chronic cough, has a treatable underlying cause. But once you've treated and evaluated for all the treatable or common causes of chronic cough, and a patient is still coughing, that's refractory chronic cough, and the prevalence of that is probably about 5 to 10% of all patients with chronic cough.

Alright, let's talk about the patient burden of refractory chronic cough. So, chronic cough has a lot of consequences in multiple domains. Clinically, many patients, especially women, will present with urinary incontinence, which can be very troubling and disruptive. Also, dizziness, headaches, and sleep disruption, either from cough that prevents patients from sleeping at night or wakes them up from sleep. This sleep disruption can lead to exhaustion and can exacerbate underlying diseases.

In addition, there are a lot of social consequences for having a chronic cough. It often interrupts a patient's speech and causes them to avoid activities or have impaired relationships with their family, friends, and coworkers. There are also patients that often report concerns that people are worried that they're going to be contagious or that they're going to spread their cough or some disease, and so they avoid activities, which leads to a lot of psychological consequences: depression, anxiety, self-consciousness, and embarrassment. Also, many patients are very worried that they may have some serious underlying condition. I can't tell you how many patients come to me with chronic cough and are very concerned about a possible underlying lung cancer or other serious diagnosis.

All of these things also have economic consequences. A big one being impaired productivity due to missed workdays and also increased healthcare resource utilization in terms of emergency department visits and even hospitalizations.

So we briefly mentioned most common causes of chronic cough, but there's actually a wide differential for chronic cough. One is smoking and tobacco use. Active tobacco use causes irritation and damage to the epithelial layer in the lungs, which causes the production of multiple cytokines, leading to inflammation, mucus production, and can be a cause of chronic cough. Asthma is a very common cause of chronic cough. Nonasthmatic eosinophilic bronchitis, which is very similar to asthma with eosinophilic inflammation in the airways, but no bronchoconstriction. And then chronic bronchitis, which we commonly define as a productive cough greater than 3 months of the year, more than 2 years in a row. Most commonly, this is due to COPD or cigarette smoking. There's also gastroesophageal reflux disease, where acid reflux is up the lower esophageal sphincter can lead to irritation and chronic cough. Upper airway cough syndrome, most commonly from postnasal drip, again leading to secretions dripping down into the posterior oropharynx, irritation of the airway, and cough. Medications can cause chronic cough. Most commonly implicated medication are ACE inhibitors, and cough can really develop at any time after initiation of an ACE inhibitor. So we always look out for that on the patient's medication list when they present with chronic cough. In your immunosuppressed patients or others, there can be chronic, more indolent infections, NTM, or other that can result in a chronic cough. Bronchiectasis is a very common cause of productive chronic cough, where there's damage to the airways, so they produce excess and too sticky mucus, and that leads to a chronic cough. In interstitial lung disease such as IPF, you can get a lot of chronic cough, and lung cancer can definitely cause chronic cough.

So, when a patient first presents with chronic cough, so a cough longer than 8 weeks, it's very important to do a thorough clinical history and examination, and consider some routine initial evaluations. So, for all patients presenting with chronic cough, it's important to ask about cough duration and characteristics. How long has the cough been going on? When did it start? What happened when the cough first started? Were you sick with a viral illness? Did you move into a new home, get a new pet? Also, asking about certain characteristics: Is it barking? Is it wet? Is it dry? Do you produce phlegm? What are some of the cough impacts and triggers? Is there anything that the patient can tell you that makes the cough specifically better or worse? What about family history? Any family history of lung disease, lung cancer, COPD, pulmonary fibrosis? All of these things are important when you're looking at your patient.

It's also important to get a sense of how troublesome the cough is, and there's various cough severity assessments that can be used in clinical practice. Most commonly, the NRS, or the Numerical Response Scale, or the VAS, the Visual Analog Scale, but also just a

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verbal reporting of how severe the patient perceives the cough can be used as well.

It's important to look at risk factors, smoking—current or former, use of ACE inhibitors or other medications that have been implicated in chronic cough, and also occupational exposures. For the physical exam, things to focus on are an exam of the posterior oropharynx, the nose, the ear, and listening to the lungs, looking for clubbing or other signs of systemic illness, and always thinking about the underlying etiology.

So, some routine evaluations for the initial workup for chronic cough most commonly involve a chest x-ray, usually a two-view chest x-ray, baseline spirometry with bronchodilator testing. Some places will do fractional exhaled nitric oxide levels, although, you know, I understand that that's not available at all centers. This is a way to assess for eosinophilic inflammation in the airways that is often seen in asthma or nonasthmatic eosinophilic bronchitis, and also a peripheral blood count looking for eosinophils, and also labs, especially looking for peripheral eosinophils on the CBC, as this can be a sign of type 2 inflammation and is often seen in airways disease like asthma.

While you're working up and treating and trying to get to the bottom of chronic cough, sometimes additional investigations are needed. If GERD, or gastroesophageal reflux disease, is suspected, sometimes an EGD is needed, or even more specialized testing like Bravo pH testing, where they leave a little capsule at the bottom of the esophagus to look for acid exposure and if that correlates with the patient's cough symptoms. Or if there is a concern for esophageal dysmotility, sometimes an esophageal manometry is needed to look at pressures in the lower esophageal sphincter and make that diagnosis. You can do induced sputum for eosinophils, especially if FeNO is not available in your area. This is also going to give you a sense of the percentage of eosinophils in the sputum, and if there's any eosinophilic signature that can suggest a diagnosis of asthma or any nonasthmatic eosinophilic bronchitis.

If there's concern for a chronic underlying or indolent infection, and a patient's having a productive cough, it's always important to get cultures if a patient has a productive cough, including a sputum AFB and bacterial culture, looking for nontuberculous mycobacteria and other standard bacteria.

Sometimes a laryngoscopy is needed to go down and actually look at the vocal cords, look at secretions, look for swelling, look for erythema or other lesions of the vocal cords that might explain or get to the etiology of the chronic cough diagnosis.

If asthma is suspected, but a patient maybe is not responding to inhalers appropriately, or the spirometry is normal, sometimes we can use provocative testing, like a methacholine challenge test, where we actually irritate, give an irritative substance to a patient, have them inhale it, and see if their airways constrict in response. Having a negative methacholine challenge test has a very high negative predictive value and suggests that the patient does not have asthma.

Chest CT if there's any concern for underlying bronchiectasis, lung cancer. Very important in immunosuppressed patients or patients with a cancer or smoking history to rule out any structural causes. And rarely, but definitely in the arsenal, bronchoscopy is sometimes used again to look for infections, endobronchial lesions, or other findings that might explain the cough.

So we mentioned some of the tools that can be used in the clinic to assess a patient's cough severity. So there's different cough severity assessments that help evaluate the intensity of cough and how much it may be disrupting daily life. Some of the more commonly used and validated assessments include the Numerical Rating Scale, which you can see here on the right. This is basically a numerical scale that goes from 0, no cough, to 10, the most severe cough, and patients will rate their cough somewhere on this 0 to 10 scale. It can also be used at subsequent visits to assess patient response to interventions.

There's also the cough severity Visual Analog Scale, or VAS, and this is a visual scale where patients rate on a scale of 0 to 100 visually the severity of their cough. And this can also be used at follow-ups to evaluate response interventions.

Other tools that can be used but less commonly are the Cough Severity Index and the Leicester Cough Questionnaire.

It's always really important before you start going down the pathway of evaluating and treating for the most common causes of chronic cough to make sure in your history that there's no red flag symptoms that might indicate a more serious cause of chronic cough. I always very thoroughly screen patients for the presence of any red flags, and obviously evaluate and treat those red flag symptoms first.

So some of the red flags would be patients that come from an area that's endemic for TB or a very high risk population, even if the chest x-ray is normal. Any patients that present with hemoptysis, that's a significant red flag that should be definitely evaluated further with high-resolution chest CT; any smokers over 45 with new cough, change in cough, or hoarseness or voice disturbance, hoarseness in general can indicate laryngeal nerve involvement or an upper airway cause that should be evaluated more thoroughly; any adults age 50 to 80 with a 20 pack-year smoking history or current smoker, very prominent dyspnea, particularly at rest or at night; any systemic B-type symptoms, fever, weight loss, new peripheral edema, definitely deserves further investigation and probably a chest CT; dysphagia, vomiting, recurrent pneumonias, any abnormal respiratory exam or abnormal chest radiograph. And usually the first step with almost

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any of these findings is a high-resolution CT scan, and then further workup directed based on the symptom, i.e., sending to an ENT for laryngoscopy for hoarseness or GI to evaluate for esophageal problems if the patient is presenting with dysphagia or vomiting.

So once you've ruled out red flag symptoms, then you can get into investigating the more common etiologies of chronic cough. So this is really the pathway you're going to take in patients with chronic cough who are nonsmokers, not receiving ACE inhibitors, have a normal or stable chest x-ray. Then you really want to look at, evaluate, and treat these three most common causes of chronic cough.

So the first thing you want to evaluate and treat for is upper airway cough syndrome. So this can include allergy testing, either IgE-specific blood allergy testing or skin testing through an allergist. Empiric treatment of any allergies that are found with guideline-directed allergic rhinitis therapy. If a patient has symptoms of chronic sinusitis, a history of polyps, any problems with smell or anosmia, sinus imaging is indicated again to get a better sense of polyps, any chronic rhinosinusitis that might need to be addressed. And then sometimes, if the sinus imaging abnormal, or if there's other concerns, patient can be referred to an ear, nose, and throat doctor to consider a nasolaryngoscopy to better evaluate the sinuses and for causes of upper airway cough syndrome.

The next most common cause of chronic cough is asthma or nonasthmatic eosinophilic bronchitis. For this workup, you want to start with your basic spirometry, often with a bronchodilator challenge to see if there's any reversibility that would be suggestive of reactive airways disease. You can look for sputum eosinophilia or perform a fractional excretion of nitric oxide if available to look for sputum or airway eosinophilia that may be addressable. Peripheral eosinophilia on a CBC with differential can be helpful as a suggestive marker of type 2 inflammation that may indicate underlying asthma if elevated. And if the diagnosis still remains in question, there's always bronchoprovocation challenge testing that can be done, such as the methacholine challenge test, which was mentioned previously.

Then, for gastroesophageal reflux disease, it's always recommended if a patient has symptoms of acid reflux as well as cough, to trial a proton pump inhibitor for at least 8 to 12 weeks. And then withdrawal is always important if there's no benefit. Consider a referral to your gastroenterology colleagues for further workup as well, including endoscopy, Bravo pH monitoring, or other esophageal acid monitoring or impedance monitoring if there's concerns about ongoing reflux or esophageal dysmotility.

And how do you decide which cause of chronic cough to start evaluating and treating first? Well, the history in this sense can be very helpful. There are certain predictive clinical features for the most common causes of chronic cough that can be helpful when deciding which avenue to pursue first in your workup for patients presenting with chronic cough.

So for asthma and nocturnal cough alone, a cough that just wakes you up at night from sleep or earlier than usual in the morning is actually not very sensitive, but highly, highly specific for a cough related to asthma. In terms of gastroesophageal reflux disease, cough after meals, heartburn, and belching are all mildly sensitive, but have a very high specificity for a cough-related gastroesophageal reflux disease. And for upper airway cough syndrome, a history of sinusitis and the feeling of postnasal drip again are mild to moderately sensitive, but more specific for a cough related to upper airway cough syndrome. And rhinitis or sinusitis related symptoms is quite sensitive, but a little less specific for the same diagnosis of upper airway cough syndrome.

Now, introducing Tiffany, a patient with RCC. So Tiffany is a 55-year-old woman who presents to your office with a chronic, dry, nonproductive cough that's been going on for the past 3 years. She's a lifetime nonsmoker and has no family or personal history of lung disease. She has occasional throat clearing and a globus sensation, mild nasal congestion, but it mostly presents seasonally, mostly in the spring during weed season. She has episodic heartburn, maybe one to two times per week. It can get worse after late meals. She has no wheeze, chest tightness, no exertional dyspnea suggestive of uncontrolled asthma. She doesn't make purulent sputum. She denies any B symptoms. No recurrent infections. She's not on an ACE inhibitor or any other culprit medication. And when you ask her to rate her cough using the NRS, she reports a cough severity of 8 out of 10. It's very disruptive to her daily life.

So, what's the timeline for assessing refractory chronic cough? The patient comes to you, and in those first 4 to 6 weeks of that first visit, you're going to reduce and manage the risk factors, look at her smoking history, evaluate and make sure she's not on any ACE inhibitors or other culprit medications, investigate environmental stressors or triggers, changes in the home, again, new pets, anything like that. Then you'll start sequentially treating for and evaluating the most common underlying conditions after you've ruled out any of those red flag symptoms that we talked about earlier. Depending on the initial evaluation and clinical features that come out during that initial visit, you'll start by picking one condition and empirically evaluating for and treating that condition for about 2 to 4 weeks per condition, especially for upper airway cough syndrome and asthma or NAEB. For GERD, it does often take a little bit longer, maybe 2 to 3 months for treatment effects to appear in terms of improving chronic cough. So that might take a little bit longer.

What's really important is not to just keep adding therapies. So the most important thing I find is that you sequentially evaluate and treat for one condition, give it a really good try, but it's so important not just to keep adding up polypharmacy, but to sequentially also peel back ineffective regimens. And then you can still consider additional investigations as time goes on if your initial approach or evaluations and treatments don't yield benefit. And we've talked about many of these before.

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So, what are the current unmet needs in refractory chronic cough? Well, I think the big one is that there's currently no FDA-approved therapies for refractory chronic cough. Clinical practice these days—and I'll tell you it's definitely true for my practice—relies on off-label neuromodulators. And these agents have a lot of side effects: dry mouth, sedation. Also, often patients go years without diagnosis and have a lot of trouble or delayed access getting into multidisciplinary cough clinics. There's not a lot of those out there, and there's also very few people who specialize in chronic cough. As we've talked about before, chronic cough has a lot of consequences and can lead to a severely decreased quality of life that can persist given delayed access to medications and the fact that there's no currently FDA-approved therapies.

So, what are our takeaways? Evaluation for any patient presenting with chronic cough should begin with a very careful history and physical exam, number one to rule out red flag symptoms, and then number two to come up with the most common potential causes of chronic cough with additional testing and treatment guided by the clinical presentation. RCC, or refractory chronic cough, is a chronic cough that per- despite appropriate evaluation and treatment of the underlying causes, and it has substantial physical, psychological, social, and economic consequences for our patients. And patients without an alternative diagnosis on initial evaluation systematically assess and appropriately treat common causes, especially upper airway cough syndrome, asthma, nonasthmatic eosinophilic bronchitis, and gastroesophageal reflux disease before diagnosing RCC. RCC should really only be considered when the cough persists despite optimal treatment, and when really no further investigations can be considered or are indicated for the workup of cough. Validated tools such as the Numerical Rating Scale can help quantify disease burden and assess response to therapy after different interventions.

So now we're going to start and get into our second section, describing the underlying pathophysiology of refractory chronic cough. So in refractory chronic cough, there's often an initial trigger. That most commonly is a viral infection, but could also be cold/dry air, smoke, or other environmental exposures, strong odors, or some type of untreated upper airway cough syndrome, GERD, or asthma. And basically, what happens is there's a reprogramming of the sensory inputs to cough.

So as you can see here on the right, there is a graphic that shows the difference in the urge to cough and the stimulus intensity for patients with chronic cough and the so-called normal patients. So basically, A on the x-axis here is a mildly tussive stimuli, so a stimuli that has a mild ability to produce a cough. For normal patients, this kind of mild stimuli will not even induce an urge to cough. But for a chronic cough patient who has a cough hypersensitivity, even that low-level mild stimuli will elicit the urge to cough, but it's not high enough to actually surpass the motor thresholds to elicit a cough.

Then you move to stimulus B, which is your moderately tussive stimuli. So this is the kind of stimuli that a normal person would actually elicit a urge to cough, but not be strong enough to actually make them cough. But for someone with chronic cough, even this moderate stimuli will elicit both the urge to cough and actually produce a physical cough. It actually takes a strong tussive stimuli to actually pass that motor threshold and elicit a cough in a normal patient.

So now, we're diagnosing Tiffany with refractory chronic cough. On her initial assessment and baseline evaluation, her history and physical exam, with her smoking status, medications, exposures, and red flags reviewed, was unrevealing. Her chest radiograph is normal, and her spirometry with bronchodilator is normal with no bronchodilator response. She's been treated empirically for the three most common causes of chronic cough. For her upper airway cough syndrome, she used an intranasal corticosteroid and first-generation antihistamine for 8 to 12 weeks, and there was minimal change in cough. She was treated with a moderate dose inhaled corticosteroid and long-acting bronchodilator for 8 to 12 weeks with no response. And her blood eosinophils, FeNO, and sputum eosinophils all came back normal. For GERD and LPR, she adhered to lifestyle measures and a daily proton pump inhibitor as well as alginates after lunch and dinner for 8 to 12 weeks, and her heartburn improved, but there was no effect on her cough. You've also evaluated her for less common causes of chronic cough, given her lack of response to these common interventions.

So a CT chest was finally performed after 3 years, and it was normal with no interstitial lung disease, bronchiectasis, or masses. She was referred to ENT and underwent laryngoscopy, which showed only mild laryngeal erythema, probably just from coughing. There were no structural lesions or vocal cord dysfunction, and other causes were excluded, including chronic infection, aspiration, heart failure, and neuromuscular disease. So you've now decided and come to the conclusion that Tiffany has refractory chronic cough. She has a cough that persists despite completing a full guideline-directed evaluation and treatment.

So now I will hand it over to my colleague.

Dr. Dicpinigaitis:
Well, thanks very much, Lauren. Dr. Eggert just went through a very nice summary of chronic cough, its epidemiology, its clinical manifestations, the effect on quality of life a chronic cough can have, how to diagnose and treat a chronic cough, and how to finally get to an appropriate and correct diagnosis of refractory chronic cough when that chronic cough has not responded to the known underlying causes of chronic cough.

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Once we're at refractory chronic cough, it's very important for us to understand that refractory chronic cough, or RCC, is its own distinct medical condition. This is no longer a cough due to something else, but it is a manifestation of vagal nerve reflex hypersensitivity, which causes enhanced cough reflex hypersensitivity, and thus causing this cough that we cannot treat with normal interventions.

So the cough reflex can become overstimulated by inflammatory stimulation of the airway, but also the airway itself can become hypersensitized peripherally due to inflammation, due to airway injury. And we've learned over the last decade or so that there are certain very important molecular pathways that we'll get into in more detail, but those include the purinergic P2X3 receptors and the transient receptor potential vanilloid, or TRPV, receptors. They're both central peripheral components to the cough, but as we remember learning in medical school, there is a trigger in the airway that begins the vagal afferent signal to the brain. But we learned in medical school, it's basically lung to brainstem, brainstem causes cough, and that's all there is to it. Well, we now know there is much more to it, and that cough is very relevant above the brainstem, and we'll get into that shortly.

But we've learned a lot over the last decade about how complicated the peripheral stimulation can be. Yes, it's a simple reflex stimulation in the periphery, brainstem causing cough, but there are many different receptors and ion channels in the airway that can be stimulated to begin that vagal afferent signal up to the brain. And we know that various receptors, as you see in the figure there, are relevant: the P2X3, as I mentioned, are very important, TRPV1, TRPA1, TRPV4, TRPM8, the voltage-gated sodium channel blockers are all relevant. So even though cough might be a simple reflex, what's not simple is that there are many different receptors that can be stimulated in airway to begin that afferent signal.

So we've learned recently that ATP is a very important mechanistic factor in beginning the afferent signal of cough to the brain. So the P2X3 receptors are ubiquitous sensory afferent receptors, and they're quite present in the airway. And what we've now learned is that when you have situations of increased ATP in the airway, that can happen with airway inflammation or other airway injury, the increased amount of ATP in the airway stimulates the P2X3 receptors to begin the afferent signal to the brain for cough, and this has then therefore led into the development of P2X3 receptor antagonists as potential cough drugs, which we'll mention shortly.

So not only is there increased stimulation of the airway peripherally because of inflammation in the airway, increased ATP in the airway, triggering the P2X3 and other receptors, but we now, in this study looking at an airway biopsy, have this very useful, really pathological correlate to what's going on in our RCC patients. So on the left, you have an airway biopsy staining for epithelial sensory nerves, but in the diagram on the right, this is an airway biopsy of a patient with RCC, and you see there's an enhanced density and an increased branching of these airway epithelial sensory nerves. So there really is a anatomical underlying basis for our patients with RCC.

Now, as I mentioned, we learned that in medical school it all stops at the brainstem, and we now know that is not correct. So some very interesting experiments have been done by Dr. Mazzone in Australia, and what he did was the following: He had his patients on a functional MRI table, and he had them inhale capsaicin, which is what we use in the lab to induce cough. Capsaicin comes from the red hot chili pepper. And in this experiment, he had subjects on the MRI table, and he gave them concentration of capsaicin that did not induce cough but induced the urge to cough sensation, that tickle or scratch in the throat telling you that you know there's a cough coming. And when he induced the urge to cough sensation in these patients, he saw multiple cerebral areas lighting up. So clearly, the cough experience goes above the brainstem, beyond a simple reflex to having central involvement. So there's a hypersensitization peripherally, as we discussed, but there's also a hypersensitization or a neuromodulation or a plasticity centrally.

So there's something else going on centrally. Not only is this hypersensitization centrally, but there's also a loss of inhibition. So, what you can do in the laboratory, for example, is you can have somebody inhale capsaicin. And if you have a non-coughing, otherwise healthy volunteer, you can tell them, even though you feel the need to cough, try to stop yourself from coughing. And a non-coughing healthy volunteer can, to a good degree, prevent themselves from coughing even when giving the stimulus. And we can suppress cough if we're not RCC patients. You know that when you go to the theater or to a concert, not too much coughing going on during the procedure, and as soon as intermission hits, everybody's coughing and clearing their throat like crazy. But in patients with RCC, they lose that central inhibition to suppress cough to any degree.

So you see now how complex this RCC neurophysiology is, and it explains why it's so difficult to treat patients with RCC. Not only do you have a peripheral hypersensitization, but you also have a central hypersensitization and a decrease in central inhibition, all leading to that difficult cough that we all struggle with with our RCC patients.

So to summarize this section, as I mentioned, refractory chronic cough really needs to be looked at as its own distinct medical condition manifesting cough reflex hypersensitivity. There are both peripheral and central pathways contributing to this refractory cough. The peripheral sensitization often involves the P2X3 receptors, as we learned, but there also are other receptor ion channels in the airway that could be the initial trigger of that afferent cough reflex, and the central sensitization may be what explains why, for example, our patient with chronic cough for 3 years remembers their cough started with what seemed like a simple common cold 3 years ago. The

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cold came and went in a week, as did all the other symptoms, except our patients are left with this dry, persistent cough every single day for years, probably because of this multifaceted hypersensitization that went on because of that viral infection.

Well, when we do get finally after doing the appropriate workup, as described by Dr. Eggert—once we do make the appropriate diagnosis of refractory chronic cough, and that's what we're dealing with, what are our options at this point in time? And unfortunately, our options are not good. In fact, we have no good options. In the United States, we have no approved drugs for RCC. So what we as clinicians are left with is to use off-label medications to try to help these poor patients. Opioids are commonly considered as antitussives: morphine, codeine, hydrocodone, or the classic mu opioid receptor agonists. Obviously, this is not a very satisfactory option for something that may be chronic therapy. So, what many of us, including myself, do is we use one of the so-called neuromodulators to try to suppress this hypersensitive cough reflex. And I typically begin with a course of amitriptyline, and then if that's not successful, move on to a course of gabapentin. Unfortunately, in my experience, both of these drugs are not very effective against cough.

But the other challenge is that not only do these drugs need to improve a patient's cough, but the patient has to tolerate the dose of the drug that gives them cough suppression. And especially with gabapentin, this is very often not tolerated. So we really desperately need drugs for RCC. There is a drug ex-US called gefapixant that has been approved elsewhere: in Japan, in the European Union, and we'll talk about gefapixant in a moment.

So it's not only drugs, but we have learned in the last 10-15 years or so that our speech-language pathology colleagues can be very instrumental as part of the RCC treatment team. And there's at least one randomized controlled trial showing that speech-language pathologists can improve the outcome of RCC. So what our speech therapists refer to as behavioral cough suppression therapy is what they do, and really it's a multimodal approach where the speech pathologist sits down and speaks to the patient about cough, gives them education about cough. Then they go through various breathing exercises, various attempts at what we call vocal hygiene so as not to irritate your larynx by shouting or certain types of loud talking. Also, trigger awareness. It was mentioned that patients with RCC have triggers that make them cough that don't make the rest of us cough. And those common triggers for RCC, and you should ask this when you see these patients in the office, they will cough because of change of air temperature, going from warm to cold, cold to warm, strong smells, deodorants, perfumes, household detergents, and then mechanical activities like laughing, singing, talking, very common cough triggers.

So this is discussed with the speech language pathologist. So it can be very useful.

Unfortunately, there are still very few speech-language pathologists that are interested in an expert in chronic cough, but we're hoping to get more of these colleagues into the fold to help us with these very difficult patients.

Coming back to our patient Tiffany, who has been appropriately diagnosed with refractory chronic cough, and she carries that diagnosis because she has been treated with empiric drug trials against upper airway cough syndrome, against drugs for asthma, nonasthmatic EB, and reflux. So at that point, she was started on amitriptyline. She had some, not much of an effect on the cough, but also a very dry mouth. She subsequently was tried on a trial of gabapentin, but as is often the case, even before getting to the target dose of gabapentin, she found the degree of sedation intolerable, and she was referred to a speech-language pathologist for behavioral cough suppression therapy. She inquired whether she should travel to get gefapixant that's not available in the U.S. Well, given where we are in the states right now, certainly if there are any clinical trials being conducted near you for which your patient may be eligible, then that's always a good idea to direct them there.

Now, this is one study that was presented at the American Thoracic Society meeting just this past spring. A real-world survey, really, of what are clinicians doing out there with these difficult patients with RCC and what has been their experience? And as you see in the table there, various trials of drugs had very little effect on response. I mean, the opioids did best, but of course they have all of the negative baggage there. So, as I already mentioned, we do not have a good option for RCC at this point in time, and we desperately need better therapies.

Now, thankfully, because we've learned so much about the mechanism of cough over the past 10-15 years, and we've learned about the relevant receptors and ion channels in the airway, once you identify those relevant receptors, you can then look for antagonists, or in some cases, agonists, to these receptors that might be chronic cough medications down the line.

So this is a list of programs going on at the moment in various levels, stages 1, 2, and 3. But I'll go through just a few because of constraints of time. So these are some of the drugs that are being looked at. Unfortunately, camlipixant, which is the second P2X3 antagonist that came out after gefapixant, we just learned, unfortunately, in July that the phase 3 studies, one of two was negative, and that program is being discontinued. But there are other drugs in the pipeline that I'll mention briefly.

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So again, looking at the anatomy now of what we know the cough reflex and the cough experience is, you know, you can target both peripherally and centrally. And on the right hand, you see the aforementioned receptors and ion channels that we've identified. So drugs have been actively developed against those: camlipixant, gefapixant, and now relicapixant against the P2X3. We have nalbuphine, which is a centrally acting drug, taplucainium, which is a voltage-gated sodium channel blocker, and interestingly, a drug still called SCO32. It's actually it's not a drug; it's a alkaline salt of magnesium, and it's been shown that these divalent cation salts increase or they hydrate a dehydrated airway, and thereby it's been shown already in early studies that that decreases cough and cough reflex sensitivity. So great interest in what we may learn about that particular molecule.

So, just to briefly mention, the first phase 3 study for cough ever done was looking at the P2X3 antagonist gefapixant, and unfortunately, as the first ever phase 3 trial done, there was a tremendous placebo response in this study. Now we had gotten used to a 30% placebo response in prior cough studies, this had a much larger one. Despite the fact that there was a huge placebo response, the 45-mg dose of the drug still had a statistically significantly effective improvement in objectively measured cough frequency. And on that basis, and because the drug is totally safe, regulators in Japan and Europe approved the drug, but FDA on two occasions declined to approve this drug, so we don't have it. We will not have it.

We then were looking forward to the second ever phase 3 study, which was camlipixant, which was a more specific P2X3 antagonist. And the two phase 3 studies that were just completed were called CALM-1 and CALM-2. And we learned, sadly, just this past July that one of those two studies came in negative, and the company decided based on the data they had, the full dataset has not yet been released publicly, but this decision has been made not to further pursue this program, unfortunately. And this is just as I mentioned, one of the two phase 3 studies did have a positive endpoint, but the other one did not. So camlipixant will not be looked at further.

Now, on the positive end, there's an interesting molecule called nalbuphine, which has completed phase 2 studies both in refractory chronic cough and in idiopathic pulmonary fibrosis, or IPF-associated cough, which is a very difficult cough to treat, and in both of those early phase 2 studies, the drug was strongly positive.

Interestingly, nalbuphine is an opioid, but unlike the opioids with which we're familiar, which are morphine and codeine for example, those are mu opioid receptor agonist. And because of this mu opioid agonism, that's where we get into the issues with sedation, addiction, constipation, etc. Nalbuphine, interestingly, is a kappa opioid agonist, but a mu opioid receptor mixed agonist antagonist. So the hope here is to maintain the cough suppression effect of the opioid through the kappa receptor, but to have less of the unwanted side effects of our classic mu opioids. So as I mentioned, we had very impressive data both in RCC and IPF cough, and now nalbuphine is being looked at as we speak. It's just entering a phase 3 study for IPF cough and a larger confirmatory phase 2b study for refractory chronic cough.

Now I mentioned taplucainium, which is a voltage-gated sodium channel blocker, kind of like a lidocaine drug. It's an inhaled drug, and we were looking forward to phase 2b data from this drug, and unfortunately, we just learned last month in August that, in fact, the phase 2b study of taplucainium also did not yield a positive result. So it was not a great summer for chronic cough.

Leaving drugs, our ENT colleagues have recently been doing more and more superior laryngeal nerve blocks in patients with RCC. Unfortunately, we don't yet have a randomized controlled trial to really assess. We have case studies, case reports, and certainly there are patients that do benefit from the procedure. The patients I see in my office, I'm seeing because they haven't had a good outcome with a nerve block, and they're coming to see me, but the experience appears to be that oftentimes patients will get relief, but it'll be partial and transient. But as we gain more experience, hopefully we'll be able to put together a proper RCT to really get our hands on how important this mode of therapy can be for our patients.

So, by its very nature, chronic cough is very much multidisciplinary. Oftentimes, the pathway is our chronic cough patients start with their primary care doctor. The primary care very variable in terms of how far they'll bring that initial assessment along before referring. And when the primary care physician decides to refer, they can refer either to pulmonary allergy, ENT, a GI, depending maybe on where their suspicions lie.

So oftentimes, a chronic cough patient will see multiple physicians along the route, but it's always best to try to coordinate care as much as possible because with these patients with chronic cough, especially in my experience running a cough center, I very often see patients who've been coughing every day for 10, 15, 20 years and have gone through multiple rounds of different primary care doctors referring them to a host of specialists who then repeat the studies that they don't need repeated, either because time has gone by or there's not an electronic medical record where physicians can access what's been done before. So oftentimes, unfortunately, patients have had multiple CAT scans, multiple spirometry, multiple EGDs, etc. So to have a coordinated care approach to our patients with chronic cough, not only will benefit them in terms of hopefully getting to an earlier diagnosis, but should save massive amounts of money and effort just by not repeating diagnostic studies that don't need repeating.

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When we see the patients with chronic cough, especially the folks I see in a chronic cough center who have been coughing for years, oftentimes, their first reaction before I've done anything to help them is they are so appreciative of me because they say I'm the first physician who clearly appreciated how their chronic cough has been a life-changing event. So it's very important for us as physicians not to underestimate what a tremendous burden chronic cough can have, not only on the patient, but as you can imagine, the patient's spouse, family, co-workers. There's a whole network of sufferers around these chronic cough patients.

Setting expectations is very important, right? We're not going to aim for okay, I'm going to make your cough go from 100% bad to 0. We're not going to say that because we don't anticipate that, but neither do our patients. Oftentimes, our patients will always agree with us that we're not going to magically wave a wand and make your cough go to 0. They just want an improvement in cough so that they can maybe not cough for 2 or 3 hours. Why? Because that lets them go to church. That lets them go to their child's concert or to a restaurant for an hour or 2. So that's a life-changing experience. The other reason why a partial effect can have a massive effect on a patient is, as Lauren mentioned, women with chronic cough very frequently have cough-induced stress urinary incontinence. In fact, we published a study out of our place showing that 62% of women coming to see us have cough-induced stress urinary incontinence. Now, stress urinary incontinence happens usually after a long series or bout of severe coughing. So, in that patient, you can improve the cough by 50%, but if that 50% takes away that severe bout of coughing, you can eliminate the urinary incontinence by 100% in a patient just by making the cough better by 25 or 50%. So setting expectations is very important on both sides.

So again, our takeaways from this section: unfortunately, we do not have any approved drugs for refractory chronic cough in the United States, so we use off-label drugs. We have to be aware that they are often not effective and often not tolerated. Thankfully, we've learned a lot more about RCC recently, and that has directly led to new drug development trials and more insights to us physicians as to why our patients are coughing. It's not only about drugs. Remember, the speech-language pathologist can be very useful. And as we go through these various drug protocols with our patients, it's going to be shared decision-making in terms of what the patient wants to try and what the patient can tolerate.

Overall key takeaways: remember, RCC is its own distinct medical condition. It's its own disease. It's not something due to something else. It's a manifestation of cough reflex hypersensitivity. There are multiple potential peripheral targets in the airway that begin the afferent cough signal, but we now know that there are both peripheral and central mechanisms of hypersensitivity and decreased inhibition that then allow the manifestation of this very difficult to treat RCC.

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